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The British Journal of Surgery

Volume 77 Number 2 February 1990

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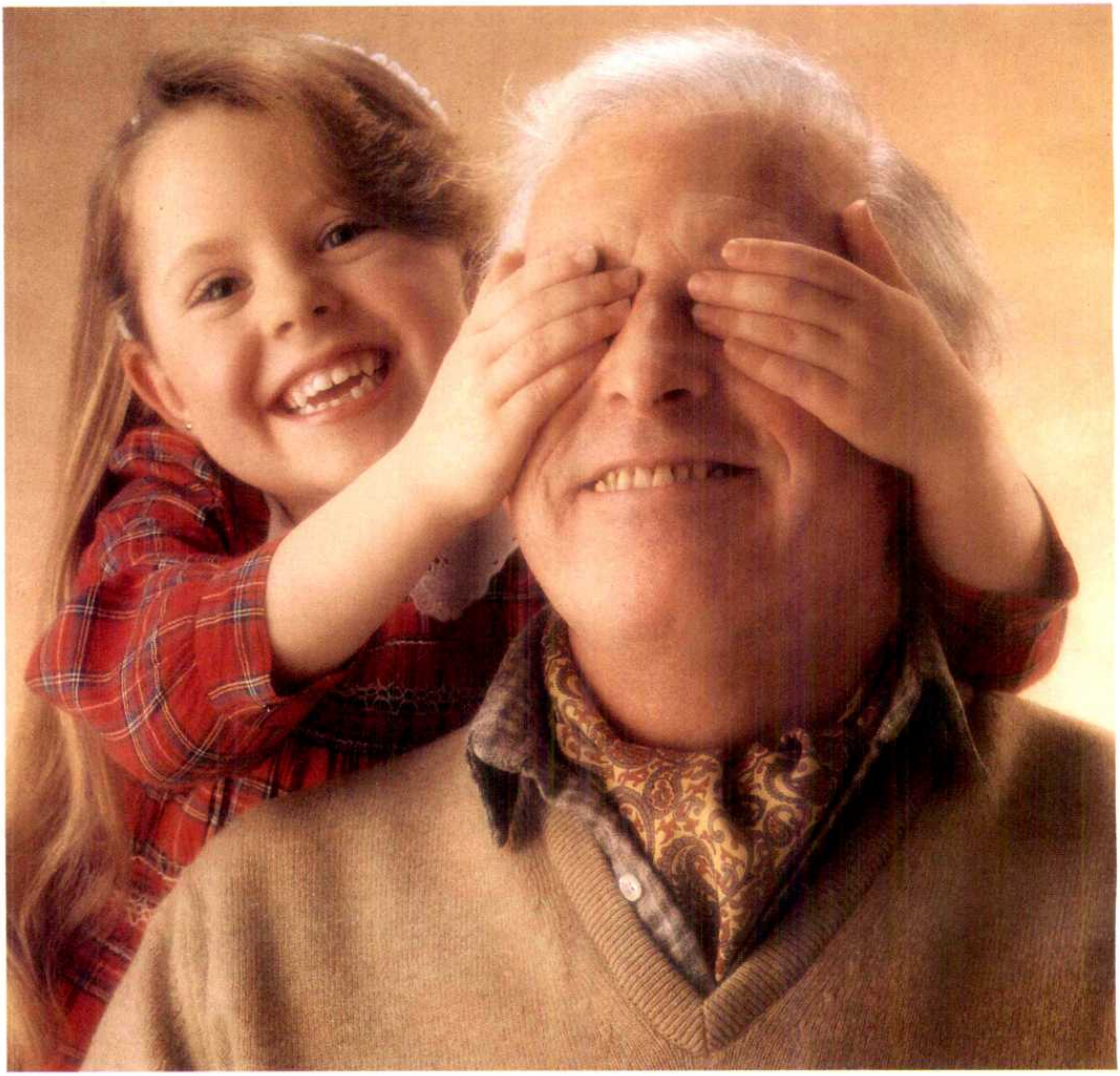
Guess which prostate cancer treatment most patients would choose.



In a recent study[1], 57 prostate cancer patients were invited to participate in choosing their treatment. All were informed that the two treatments available, sub-capsular orchidectomy or 'Zoladex', were similar in efficacy and side effects. 49 of the patients (86%) opted for 'Zoladex'.

A recent trial[2] has established the equivalence of 'Zoladex' to orchidectomy.

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Reference 1. Lunglmayr G, Girsch E. In Chisholm G D ed. *'Zoladex' – a new treatment for prostatic cancer. International Congress and Symposium Series.* 125. London: RSM Series, 1987: 47-51.
2. Peeling W B. ibid: 27-46.

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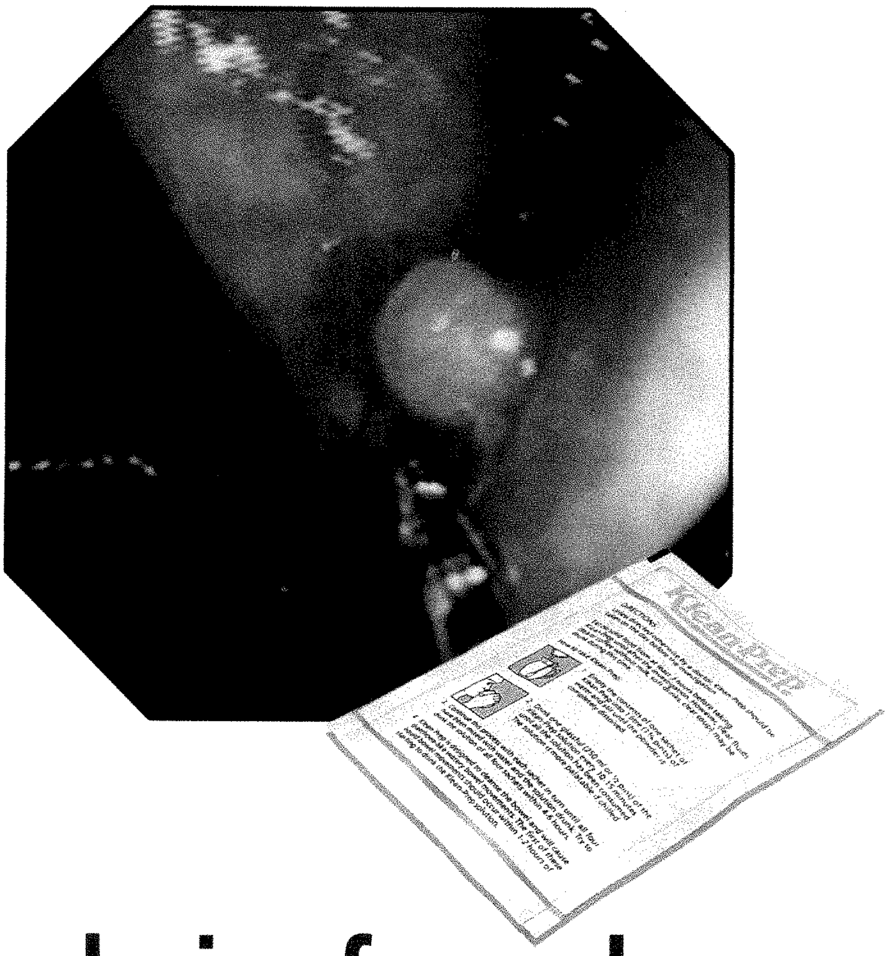

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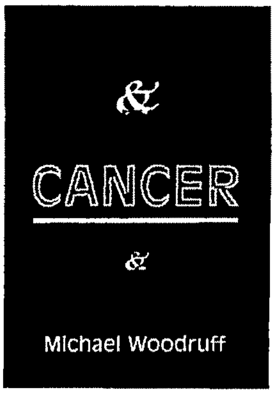

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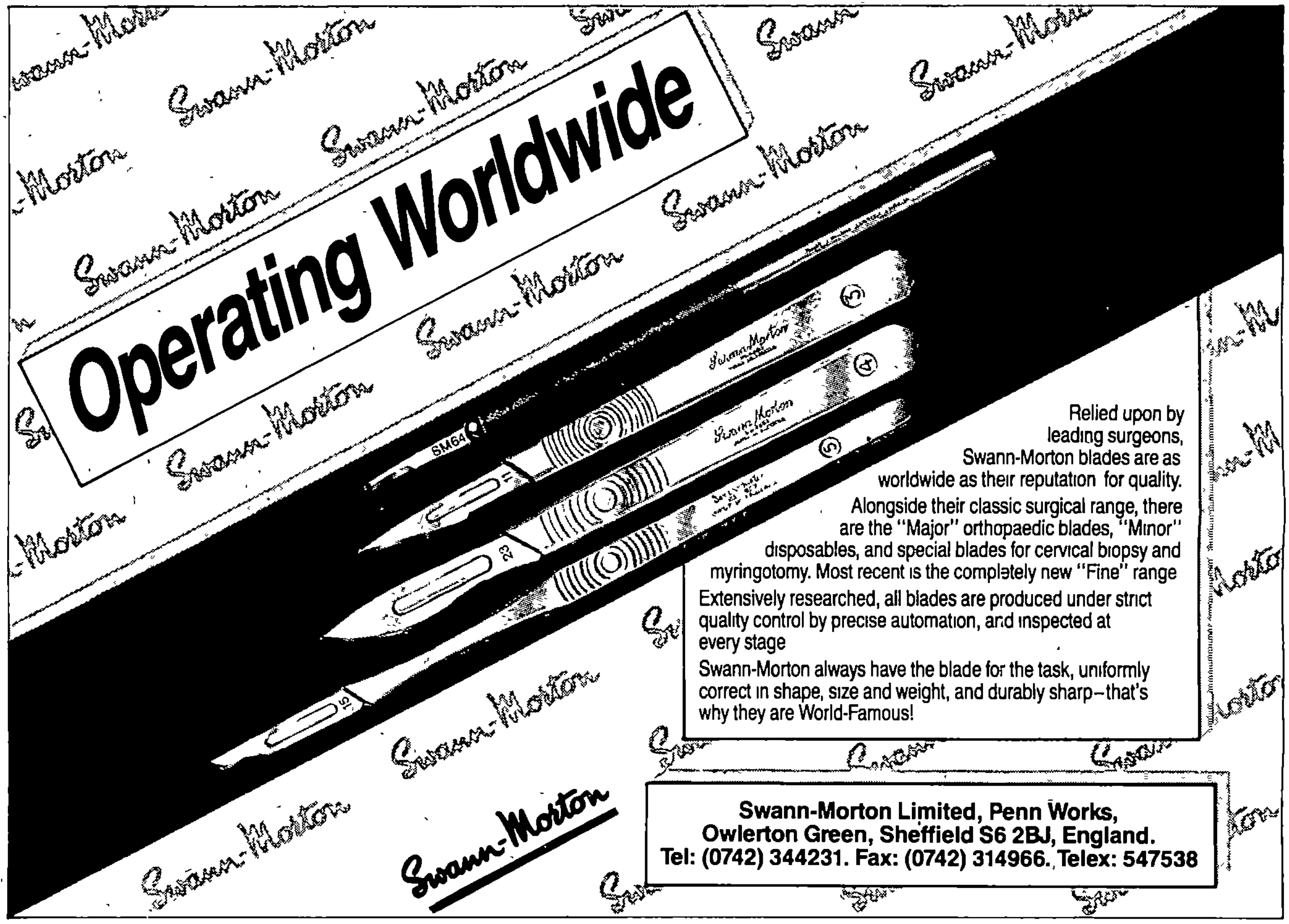

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Pancreatic pain

Although pain is one of the main symptoms of acute and chronic pancreatitis as well as pancreatic carcinoma, until recently little interest has been shown in its pathophysiology. There are reasons for assuming that pancreatic pain has many causes, and it has long been thought that increased intraductal pressure is one of them. This theory was initially supported by intraoperative, and later by endoscopic, measurements. Japanese investigators[1], using an endoscopic technique, found higher intraductal pressures in patients with painful chronic pancreatitis than in those in whom it was painless. A new technique for intraoperative, as well as percutaneous, measurement of pancreatic tissue fluid pressure has recently been developed in Denmark[2]. A close correlation was found between tissue pressure and pain in patients with chronic pancreatitis who underwent drainage operations. A substantial reduction in pressure after drainage was followed by relief of pain. In patients with recurrent pain, however, the pressure again increased.

Another group of authors have put forward a new concept that they have called 'pancreatitis-associated neuritis'[3]; they reported a comparative increase in the number of nerves in inflammatory pancreatic tissue, together with round cell infiltration and a striking disintegration of the perineurium. They suggested that loss of function of the perineural barrier allowed an influx of inflammatory mediators or active pancreatic enzymes, and they recently showed an increase in the neuropeptides substance P and calcitonin gene related peptide within sensory nerve fibres in patients with chronic pancreatitis[4].

One might speculate that these two mechanisms could work together, as high tissue fluid pressure would facilitate influx of inflammatory mediators into the nerves. Though this could explain persistent pancreatic pain, the acute episodes of pain that occur in the early stages of typical chronic pancreatitis might possibly be caused by recurrent autodigestive necrosis and enlargement of pseudocysts. In addition, sensory nerve endings in the periglandular tissue may react to chemical and physical disturbance and contribute to pain sensation while the pathological processes within the gland are progressing. It has become more and more obvious that it is difficult to correlate pancreatic pain and morphology, be it by gross inspection, by histological examination, or by imaging. This indicates that pain may be associated with the dynamics of the disease rather than with a static situation, an idea that fits well with the possible causes of persistent and recurrent pancreatic pain already mentioned. It also accords with the concept that pain relief may follow progressive pancreatic dysfunction or 'burning out' of the gland, which seems to occur in a small group of patients with chronic pancreatitis.

Most of our knowledge about pancreatic pain concerns that found in chronic pancreatitis, whereas the origin of the severe pain of pancreatic carcinoma is mainly speculative. The role of the perineural growth found in this disease is not clear, as it is also seen in patients without pain. To some extent, however, pain in both pancreatitis and cancer might be explained by mechanisms similar to those already described.

Apart from insisting on total abstinence from alcohol, the treatment of pancreatic pain includes giving both opioid and non-opioid analgesic drugs as well as non-steroidal anti-inflammatory drugs, tricyclic antidepressants, antineoplastic agents, and prednisolone. Lately, oral pancreatic enzyme supplements have been shown to relieve pain in about half the patients tested[4]. This is probably the result of the effect of trypsin on pancreatic secretion, which has been shown to exist in man as well as in experimental animals; the lack of trypsin activity within the intestinal lumen causes hyperstimulation of the gland by cholecystokinin, and perhaps also by cholinergic, pathways, which might lead to high intraductal and tissue pressure and pain. Conversely, restoration of intraintestinal trypsin should result in relief of pain. It might be worthwhile to give patients a therapeutic trial of enzyme supplements for 1 or 2 months, provided that a preparation known to increase intraduodenal trypsin activity is used.

A number of groups have recently reported promising results after endoscopic stenting of the main pancreatic duct in chronic pancreatitis, and the dorsal duct in

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pancreas divisum[5,6,7]. This is another approach based on the duct–tissue–hypertension theory. As only the main duct is decompressed, however, persistent or recurrent pain may be explained by continued outflow obstruction from secondary or tertiary ducts. Only prospective randomized trials will define the place of such treatment in the management of chronic pancreatitis.

Coeliac plexus block is yet another way to achieve relief of pain. Several different techniques have been described, and either alcohol or phenol should be used as the neurolytic agent. Based on our current knowledge, coeliac plexus block should be considered in pancreatic cancer more often than it is today, and at an earlier stage. Pain in chronic pancreatitis, however, should be treated by neurolytic block only as a last resort, as reported results are disappointing.

Surgery is effective in relieving pain in about 70 per cent of cases operated on[8], but careful selection of the patient, the procedure and the surgeon are important. There are two reasons for treating pain by operation; parenchyma saving operations aim to reduce duct–tissue pressure, whereas the other operations aim to remove the inflammatory, cystic, or fibrotic tissue that is thought to be the origin of the pain. Duct decompression is best done by side-to-side pancreaticojejunostomy with the anastomosis ideally at least 8 cm long. The most favourable results of this operation are in patients with dilated pancreatic ducts. The best results of resection are seen when the head of the gland is removed. This is still most commonly done as a Whipple operation, but other operations that preserve the stomach and duodenum have been introduced. Their role in the treatment of the pain of chronic pancreatitis, however, has not yet been defined. Results of distal resection have not come up to expectations, and total pancreatectomy is not an attractive alternative because of the high early and late morbidity rates, and the fact that pain persists in many patients despite removal of the gland. Pain is seldom the main reason for operation in pancreatic carcinoma; it would, however, be interesting to settle – in prospective, randomized studies – the palliative value of pancreaticoduodenal resection in patients who are not curable, but who have resectable primary lesions (that is, a few metastases in regional lymph nodes or liver, or both, in addition to the primary tumour). Such a study would be ethical, as pancreaticoduodenal resection can be done with low operative risk provided that the operation is done in specialist centres.

Our ambition to understand the mechanisms of the difficult problem of pancreatic pain is growing, stimulated and assisted by the advent of increasingly advanced technology. The medical profession has a responsiblity to evaluate the different treatments that will result in a randomized, prospective manner.

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Pilonidal sinus: finding the right track for treatment

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Management of pilonidal sinus is frequently unsatisfactory. No method satisfies all requirements for the ideal treatment – quick healing, no hospital admission, minimal patient inconvenience, and low recurrence – but greater awareness of the strengths and weaknesses of existing methods would lead to improved management. Early excision of the pilonidal pit at the time of treatment of pilonidal abscess reduces the high (40 per cent) risk of subsequent sinus. Treatments for pilonidal sinus that flatten the natal cleft halve the risk of recurrence. En bloc *excision of pilonidal sinus with secondary healing should be abandoned and emphasis given to development of treatments, such as primary asymmetric closure, which have more potential. Some treatments are operator-dependent and, to achieve the best results, junior surgeons must be correctly trained and supervised. Future treatment studies must be prospective and randomized, and should compare healing time, recurrence rates beyond 3 years, nurse and hospital visits, patient inconvenience and loss of income.*

Keywords: Pilonidal sinus, pathogenesis, treatment

The ideal treatment of pilonidal sinus should provide a high chance of cure with a low recurrence rate, and should avoid hospital admission and general anaesthetic while involving minimal inconvenience and time off work for the patient. In 1985 over 7000 patients were admitted, for an average stay of 5 days, to hospitals in England for treatment of sacrococcygeal pilonidal disease[1].

Most pilonidal sinuses resolve with treatment by the age of 40 years irrespective of the method of treatment[2,3]. This encourages surgeons to believe that their method of treatment is adequate and that there is no compelling need to change. However, the average duration of symptoms from pilonidal sinus exceeds 3 years[2] and many patients endure discomfort, inconvenience, and loss of income during prolonged or multiple courses of treatment which are often left to relatively inexperienced surgeons. Although most patients are eventually cured, treatment falls short of the ideal.

Over the last 25 years many treatments have been advocated for pilonidal sinus but no consensus has emerged, and there have been few studies comparing relative treatment costs, discomfort and time off work. In this paper the rationale for, and results of, various treatments are reviewed in order to determine those that are promising and require further evaluation and those that should be discarded.

Incidence

Sacrococcygeal pilonidal disease afflicts young adults after puberty[4]. In a population study of Minnesota college students, pilonidal sinus was noted at routine physical examination in 365 (1·1 per cent) of 31 497 males and 24 (0·11 per cent) of 21 367 females[5], but proportionately more females undergo treatment and so the ratio of patients treated is closer – roughly 4:1[4]. The ratio of males:females admitted to English hospitals in 1985[1] for treatment of pilonidal disease was 1·5.1. The abscess:sinus ratio (0·7.1) was lower for males (0·5:1) than for females 1 1:1). This may be because pilonidal sinus is more likely to be complicated, requiring multiple hospital admissions, in males.

The observation that the onset of pilonidal disease coincides with puberty and that *de novo* pilonidal disease is rare after age 40 years[2,3] is compatible with an association with sex hormones which are known to affect pilosebaceous glands[6]. This may explain the earlier onset of the condition in women[7] since puberty occurs earlier in females than in males. Differences in incidence between races are also found. The incidence is highest among Caucasians and less among Africans and Asians[7]. This probably results from differences in hair characteristics[8] such as kinking, medullation, cuticular scale count and average curvature, and from different daily rates of hair growth[9] between races.

The incidence is also affected by factors that are not related to hair characteristics. During the 1939–45 war the increase in sweaty activity associated with buttock friction[10] – particularly jeep and lorry driving[11] – and reduced opportunity for personal hygiene produced an epidemic of pilonidal disease. Seventy-seven thousand American servicemen were admitted to US Army hospitals[12] where average inpatient stay for treatment was 55 days. Karydakis has noted[13] that between 1960 and 1971 the prevalence of pilonidal sinus at the time of enrollment into the Greek army rose from 4·9 per cent to 14·8 per cent. He suggests that this increase may be due to a 3·2 kg rise in average body weight among Greek army recruits. An association between incidence and obesity has also been observed among American college students[5].

Pathogenesis

There are two conflicting theories of pathogenesis. Both have implications for the extent of surgical resection thought necessary to achieve a cure.

Acquired theory

It is most likely that sacrococcygeal pilonidal infection originates within a natal cleft hair follicle which becomes distended with keratin[14]. Eccrine and apocrine sweat glands and their ducts are normally sterile, but anaerobic organisms are found in pilosebaceous follicles[15]. The distended follicle becomes inflamed and the resulting folliculitis produces oedema which occludes the follicle opening. The obstructed follicle then

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expands and eventually ruptures into the underlying subcutaneous fat to produce a pilonidal abscess. In 93 per cent of cases the direction of this abscess and subsequent secondary tracks is cephalad[16]. Millar[17], who studied the direction of hair growth in the postanal region of 112 patients, observed that where there was cephalad tracking the inflamed follicle was situated at a mean of 8 cm from the anus, but where there was caudal tracking the follicle was a mean of 4·5 cm from the anus. The direction of the sinus track always coincided with the orientation of hair follicles at the site of the inflamed follicle. Normal perianal hair distribution is in a ring around the anus pointing away from the anus towards the natal cleft. Cephalad to this there is a change in the direction of hair which then points caudally from above into the natal cleft. There were no cases in which the direction of the pilonidal track ran in the opposite direction to the orientation of hair follicles in that area. The subcutaneous pilonidal abscess then drains on to the skin surface – usually via a laterally situated track overlying the sacrum[18]. The natal cleft follicle remnant now communicates via a track extending from the hair follicle through the abscess cavity to a laterally situated granulating sinus track opening. An epithelialized tube, extending into the sinus track from the natal cleft opening, is then formed by the residue of epithelial cells present at the site of rupture of the original follicle[14]. Movement of the buttocks exerts both a suction[19] and a drilling or 'cigarette rolling'[20] effect which encourages loose natal cleft hair and debris to enter the track whenever the patient stands or sits. When hair is propelled tip first into this tube, the barbs on the hair shaft prevent it from being expelled in a reverse direction[21]. Hair and skin debris then stimulate a foreign body reaction[22]. Rarely the hair may not come from the patient[18], and a case is reported[23] in which a pilonidal sinus contained a small bird feather of the variety used in feather bedding

Congenital theory

The identification of postcoccygeal epidermal cell rests[24], dysrhaphic sacrococcygeal cysts[25] and the observation of a familial tendency to pilonidal sinus[26] led to the suggestion[27,28] that the epithelialized tracks found in adult pilonidal sinus originate as congenital abnormalities. If this is the case, it follows that removal of all epithelialized tracks down to the presacral fascia is invariably necessary to achieve a cure. However, the majority of congenital neural canal sinuses are lumbar rather than sacral[29] and most extend to the dura. Infection does occur within these congenital tracks and as might be expected this tends to occur in children[30] and can lead to meningitis[31]. Vestiges of these congenital tracks have been detected but they are lined by cuboidal epithelium – unlike pilonidal sinus tracks which are lined by granulation tissue[22]. Congenital tracks are usually situated more cranially over the sacrum than pilonidal sinuses, do not contain hair, and can often be shown to communicate with the spinal canal[32]. It has also been suggested that pilonidal sinuses could originate from a vestigial scent gland[33] similar to the preen gland found in some birds, or that it might develop following infection in an inclusion dermoid[34]. The absence of histological evidence of intermediate conditions demonstrating either of these structures prior to development of pilonidal sinuses invalidates both these theories.

Pilonidal sinus has been reported as arising in skin derived away from the midline and subsequently brought by rotation flap to overlie the sacrum[14] after previous removal of all tissue overlying the sacrum. It was similar experience of recurrence after complete excision of all tissue overlying the sacrum which originally led Patey and Scarff[35] to suggest that the condition was acquired. Advocates of a congenital origin of pilonidal sinus have suggested that sacral skin could be indrawn to form a sinus tube by tethering to the coccyx during growth. The hair follicles in this skin then produce the hair which is found within pilonidal sinuses. Patey and Scarff[35] observed that while pilonidal tracks contained hair, the track lining did not contain hair follicles. They argued that the hair, which stimulated a foreign-body reaction, must have entered the sinus from the skin surface as could happen in other places subjected to rubbing by hair – for example on barber's hands[36]. Raffman[37] reviewed the evidence for hair follicles within pilonidal tracks and could find no convincing evidence of skin appendages – hair follicles or sweat glands – within pilonidal tracks Thus the histological findings are compatible with the view that presacral pilonidal disease originates as a folliculitis and then progresses because of formation of a foreign body granuloma.

Although rarely congenital sacrococcygeal sinus may resemble pilonidal sinus, the available evidence strongly supports an acquired aetiology for the great majority of adult pilonidal infections. Thus radical removal of all tissue overlying the sacrum in order to remove all embryological remnants should not be regarded as essential to treatment.

Pathology

When considering how to treat sacrococcygeal pilonidal disease, it is important to remember that the condition is merely a particular form of foreign body granuloma[22]. Hair is found within the track in roughly two-thirds of male cases and one-third of cases in women[16] and hair fragments – surrounded by foreign-body giant cells – are frequently seen within the granulation tissue. The majority of the track and hair-containing cavity is lined with granulation tissue. Only the midline epithelial pit through which the hair enters is lined by epithelium except in rare cases of long-standing recurrence where the epithelial lining can extend further along the track[32].

The term pilonidal 'cyst' is therefore misleading since it implies that there is a cyst lining which must be excised In pilonidal cysts, the granulation-lined cavity communicates with one or more epithelialized natal cleft pits but the cavity does not open laterally on to the skin to form a pilonidal sinus A better term for this condition is 'pilonidal granuloma'.

Other hair-induced granulomas

Foreign body granulomas, resulting from penetration of the skin by hair, have also been described at other sites of skin friction[38–46]. Interdigital pilonidal sinuses produced by human hair and by sheep's wool have been reported respectively in the hands of barbers[36] and sheep shearers[47]. Unlike sacrococcygeal pilonidal disease, the pathogenesis of these conditions usually involves direct penetration of healthy skin by hair.

Risk of malignant change

Very rarely, squamous carcinoma can arise in a pilonidal sinus – usually of long-standing[48]. Giant condyloma acuminatum[49], basal cell carcinoma[50], and adenocarcinoma[51] involving pilonidal sinus have also occasionally been reported The incidence of any of these neoplasms is far too small for pilonidal sinus to be considered as carrying a significant malignant potential

Clinical course

Pilonidal abscess

A pilonidal abscess is formed if an infected hair follicle expands into the subcutaneous tissues or a pre-existing pilonidal granuloma becomes acutely inflamed. Roughly half of all cases of sacrococcygeal pilonidal disease first present with an abscess[52] which is usually situated cephalad to the site of hair follicle infection[14]. It may not be possible to identify the infected hair follicle at the time of acute abscess formation because of surrounding oedema[14]. Incision, drainage and curettage of the abscess cavity to remove hairs and debris[53,54] results in complete healing within about 1 month in over 90 per cent of cases Simple incision and drainage results in healing in 58 per cent of patients within 10 weeks[55]. Once healing has occurred, 40 per cent of patients will have no further symptoms, and a further 20 per cent will experience only minor symptoms[55,56]. However, 40 per cent of patients treated by incision and drainage for acute pilonidal abscess will develop a pilonidal sinus requiring further treatment[56]. Bascom has suggested that if the epithelialized pilonidal pit is excised via a small (7 mm) incision at about 5 days after abscess drainage[14] when the pit can usually be identified, the early recurrence rate is reduced to approximately 15 per cent.

Pilonidal sinus

A pilonidal sinus is formed when the granulation-lined pilonidal cavity drains via a sinus track which opens away from the midline as an area of proud granulation onto the skin. During an interval between episodes of inflammation, the diagnosis can be confirmed by identifying the epithelialized follicle opening within the natal cleft 4–8 cm cephalad from the anus. The sinus track then runs cephalad from this midline opening in roughly 93 per cent of cases[16], and can usually be palpated as an area of induration deep to the sacral skin. Not infrequently there may be more than one epithelialized opening within the natal cleft but the laterally situated granulation-lined opening is single in cases that have not previously undergone surgery. Pain (84 per cent of patients) and discharge (78 per cent) are the two most frequent symptoms of pilonidal sinus[7], while fever, chills and bleeding are rare[7]. Symptoms fluctuate with recurrent bouts of infection, but rarely subside completely between bouts.

Recurrent pilonidal sinus

Late recurrence of pilonidal sinus after complete healing can be produced by further hair follicle infection, but early recurrence after treatment is usually associated with granulation-lined tracks which are a consequence of chronic infection and foreign-body reaction in an incompletely healed surgical wound. The pathogenesis in these cases is no longer the precipitating inflamed hair follicle since this has usually been excised. The unhealed surgical wound is a focus for infection and skin debris, including hair, which continues the granulomatous process. Occasionally, after many years of chronic infection, these tracks can develop a squamous epithelial lining[32]. It follows that in treatment of recurrent disease, more emphasis should be given to healing or excision of tracks than to identification and excision of the midline pit.

Perianal pilonidal sinus

In roughly 7 per cent of cases[16] of pilonidal sinus the track runs caudally where it may present as perianal sepsis. Four causes of perianal pilonidal disease have been recognized: (1) a sacrococcygeal pilonidal sinus may extend into the perianal tissues[18,57] and rarely may communicate with the anal canal[58]; (2) following laying-open of a fistula *in ano*, hair may enter either the healing wound or the scar[59]; (3) hair may enter through an anal fissure[60]; and (4) hair may penetrate normal anal skin as it penetrates other normal skin to produce a foreign body granuloma[61,62]. Treatment follows the usual principles of anal fistula surgery.

Results of treatment of sacrococcygeal pilonidal sinus

There is no shortage of reports recommending the best treatment for pilonidal sinus. Virtually without exception these studies are flawed because of one or more of the following defects in study design: retrospective analysis, patient selection and exclusion not stated, lack of randomization or lack of a control group, short or incomplete follow-up, and failure to assess treatment costs and patient inconvenience. While it may not be possible to decide about what should be done for pilonidal sinus, some conclusions can be drawn from these studies about what should not be done, and about the direction of future treatment studies.

Method of analysis of published studies

The principal reports of treatment of pilonidal disease in the last 30 years have been reviewed (*Tables 1–6*). Average healing time for each treatment method given in the tables has been derived as the quotient of the total number of patient days in all studies of each method which were spent healing divided by the total number of patients treated by that method. Recurrence (*Table 7*) was divided into early (<1 year) or late (>1 year). In every evaluable study, minimum follow-up (in contrast to average follow-up) was used to assign recurrence rate to either the early or late follow-up group. Only patients actually followed up, either by clinic review or telephone, were included. Patients not followed up may fare worse[63] so results are likely to contain an optimistic bias in all cases since inadequate follow-up was not restricted to any one treatment method. The relative cost of treatment by open and primary closure methods was calculated as shown in *Table 8*. Figures assume that: 90 per cent of patients heal by first intention after primary closure and 90 per cent of laid open wounds heal within 45 days; laying open does not require hospital admission, district nurse visits open wounds every second day for one month and third day thereafter, patient's income is the UK 1988 national average[64]; and patient returns to work 21 days after primary closure and 30 days after laying open unless healing is delayed when patients are off work for 60 days. Cost estimates of medical and nursing attention, and hospital facilities are in keeping with current UK provincial rates for private medical care.

Closed techniques

Lord and Millar have described[65] an outpatient treatment where affected midline epithelial follicles are cored out under

Table 1 *Mean healing time and combined recurrence/failure rate following track debridement and excision or phenolization of epithelial pit*

Reference	Year	Number of cases	Mean time to healing (days)	Recurrence/failure (%)
Track curettage/brushing with excision of follicle opening				
Lord and Millar[65]	1965	33	<35	3
Dorton[66]	1970	31	—	3
Edwards[63]	1977	120	52	24
Bascom[67]	1980	50	21	8
Kobel and Marti[68]	1988	366	—	9·5
Phenol injection into track				
Maurice and Greenwood[69]	1964	21	>21–<42	19
Stewart and Bell[70]	1969	30	34	27
Stephens and Sloane[71]	1969	30	<14	0
Shorey[72]	1975	23	—	9
Blumberg[73]	1978	7	<21	25
Hegge *et al.*[74]	1987	48	<56	6
Stansby[75]	1989	104	61	35
Diathermy of pilonidal pit				
Flannery and Kidd[76]	1967	62	—	10

Table 2 *Mean healing time and combined recurrence/failure rate following laying open of pilonidal sinus and healing by granulation*

Reference	Year	Number of cases	Mean time to healing (days)	Recurrence/failure (%)
Goodall[78]	1961	15	—	7
Notaras[16]	1970	45	42	13
Sood *et al.*[79]	1975	23	29	43
Ortiz *et al.*[80]	1977	14	38	7
Houston[53]	1977	25	31	3
Weinstein *et al*[81]	1977	126	<60	21
Wood *et al.*[82]	1977	131	56	1
Britton *et al.*[83]	1977	42	—	8
Eftaiha *et al.*[84]	1977	175	42	1
Hodgson and Greenstein[85]	1981	10	—	6
Thomson and Lee[86]	1982	34	<60	6
Clothier and Haywood[2]	1984	12	—	8
McLaren[56]	1984	18	42	10
Bissett and Isbister[52]	1987	48	48	19
With cauterization of cavity				
Miller *et al.*[87]	1967	362	28	3
Rickles[88]	1974	227	—	4
Gage and Dutta[90]	1977	29	105	4
O'Connor[91]	1979	12	<112	0

Table 3 *Mean healing time and combined recurrence/failure rate following excision of pilonidal sinus down to sacral fascia*

Reference	Year	Number of cases	Mean time to healing (days)	Recurrence/failure (%)
Cavity left open				
Goodall[78]	1961	36	—	21
Thomas[92]	1968	10	—	10
Notaras[16]	1970	41	70	10
Lamke *et al.*[93]	1974	47	—	15
Sood *et al.*[79]	1975	28	84	14
Ortiz *et al.*[80]	1977	14	80	7
Wood *et al.*[82]	1977	143	56	1
Jordan and Meinecke[94]	1979	16	—	19
Golz *et al.*[95]	1980	160	90	6
Clothier and Haywood[2]	1984	11	—	36
McLaren[56]	1984	34	49	9
Kronborg *et al.*[96]	1986	32	64	13
With partial closure (marsupialize)				
Van Ess[97]	1965	52	24	4
Cavanagh *et al.*[98]	1970	26	28	4
Ortiz *et al.*[80]	1977	14	37	7
Abramson[99]	1978	234	26	6
Courtney and Brady[100]	1978	26	42	4
Meban and Hunter[101]	1982	31	29	3
McLaren[56]	1984	22	20	—
Duchateau *et al.*[102]	1985	123	24	9
With split skin grafting				
Guyuron *et al.*[103]	1983	58	28	2

local anaesthetic and hairs within the remaining granulation-lined track are removed by passing a small brush along the track. Brushing of the track is repeated as an outpatient at weekly intervals until the track closes. Regular dressing of the site of follicle excision is required. Results (*Table 1*) suggest that healing takes on average 42 days. Maurice and Greenwood[69] and others have advocated a similar approach except that the epithelial component of the track and any debris within is destroyed by injection of 50 per cent phenol after curettage. Mean healing time is similar (40 days) to that reported after brushing of the track and follicle excision.

Laying open of the track

There have been numerous reports (*Table 2*) of experience with laying open of the pilonidal sinus track, often under local anaesthetic as an outpatient. Marks *et al.*[77] have advised that a suitably wide excision is required to ensure that the cavity is of a shape which drains easily, thereby avoiding stasis and chronic infection. Healing of the granulating wound requires regular outpatient dressing. Results (*Table 2*) suggest that average healing time for this approach is 43 days. Average healing time is similar (36 days) with cauterization of the cavity by diathermy[87], phenol[88], silver nitrate[89], or freezing[90,91] but there is wide variation between reports.

Wide and deep excision to sacrum

The view that pilonidal sinus is congenital, involving epithelial cell rests extending both laterally and down to the sacrum, has resulted in attempts to excise completely all tissue between skin and presacral fascia. Average healing time (*Table 3*) is 73 days if

Table 4 *Mean healing time, primary healing and recurrence rate following pilonidal sinus excision with primary closure*

Reference	Year	Number of cases	Mean time to healing (days)	Failed primary healing (%)	Recurrence (%)
Leichtling[104]	1967	11	14	9	0
Cherry[105]	1968	15	14	—	—
Thomas[92]	1968	57	—	—	12
Holm and Hutton[106]	1970	50	<10	6	4
Foss[107]	1970	90	17	11	<20
Notaras[16]	1970	43	12	30	9
Schonk[108]	1971	57	16	11	4
Tetirick[109]	1971	51	—	8	0
Evangelou and Timiakus[110]	1974	43	10·5	12	—
Lamke *et al* [93]	1974	93	23	2	26
Verbeck and Bender[111]	1974	117	—	3·5	14
Sood *et al.*[79]	1975	57	50	—	11
Kam[112]	1976	63	<10	6	—
Bentivegna and Procario[113]	1977	38	10	0	0
Britton *et al.*[83]	1977	15	—	—	20
Zimmerman[114]	1978	28	14	0	0
Rainsbury and Southam[115]	1982	72	<30	8	1
Clothier and Haywood[2]	1984	24	—	—	37
McLaren[56]	1984	41	11	—	12
Kronberg *et al.*[96]	1986	33	14	—	25
Courtney and Merlin[116]	1986	81	12	—	13
Bissett and Isbister[52]	1987	57	30	—	28

Table 5 *Mean healing time, failed primary healing and recurrence following excision of pilonidal sinus with primary closure using an asymmetric or oblique incision*

Reference	Year	Number of cases	Mean time to healing (days)	Failed primary healing (%)	Recurrence (%)
Asymmetric incision					
Karydakis[117]	1973	1687	8·2	8·5	0·1
Fishbein and Handelsman[119]	1979	50	<14	6	2
Kitchen[120]	1982	45	—	13	5
Bascom[121]	1987	30	14	13	3
Mann and Springall[122]	1987	30	<16	20	0
Oblique/transverse incision					
Roe[118]	1971	8	—	0	0
Casten *et al* [123]	1973	132	<14	2	1
Farringer and Pickens[124]	1978	54	<14	11	—

Table 6 *Mean healing time, failed primary healing and recurrence rate following excision of pilonidal tissue to sacrum and skin flap cover*

Reference	Year	Number of cases	Mean time to healing (days)	Failed primary healing (%)	Recurrence (%)
Z-plasty					
McDermott[19]	1967	29	<14	0	3
Middleton[125]	1968	30	<16	0	10
Bose and Candy[126]	1970	20	<14·5	0	0
Sood *et al* [79]	1975	23	13	0	0
Lamke *et al* [127]	1979	6	<28	7	17
Hodgson and Greenstein[128]	1981	9	<14	0	0
Mansoory and Dickson[129]	1982	127	<14	4	2
Morrison[130]	1985	11	<10	20	10
Toubanakis[131]	1986	110	<14	0	0
Rotation/advancement flaps					
Hobbs[132]	1967	42	25	4	—
Lamke *et al* [127]	1979	10	<28	0	0
Fishbein and Handelsman[119]	1979	50	<14	6	2
Trooskin[133]	1985	12	10–21	0	—
Rectangular rhomboid					
Azab *et al.*[134]	1986	25	<10	0	0
Gwynn[135]	1986	20	<10	5	5
W plasty					
Roth and Moorman[136]	1977	12	<14	8	0

Table 7 *Cumulative recurrence rate following methods of treatment shown in previous tables*

	Minimum follow-up			
	<1 year		>1 year	
Method of treatment	Number of cases	Recurrence n (%)	Number of cases	Recurrence n (%)
Closed (Table 1)	729	76 (14)	312	55 (18)
Wide excision (Table 2)	207	30 (14)	337	44 (13)
Marsupialize (Table 2)	341	21 (6)	26	1 (4)
Lay-open (Table 3)	732	30 (4)	307	39 (13)
Primary midline closure (Table 4)	543	42 (8)	821	122 (15)
Primary oblique/asymmetric closure (Table 5)	956	12 (1)	60	2 (3)
Skin flaps (Table 6)	274	6 (2)	80	6 (8)

Values in parentheses are percentages

Table 8 *Treatment cost and loss of income for a group of 100 patients following treatment of pilonidal sinus by laying open as an outpatient compared with inpatient primary closure Assumptions made in calculations are given in text*

Costs	Lay open		Primary closure	
		£		£
Hospital				
bed (£160/night)		nil	7 nights	112000
surgeon (£250/operation)		25000		25000
anaesthetist (£75/operation)		nil		7500
Nurse home visit including dressings (£10/visit)				
90 patients	20 visits	18000		nil
10 patients	27 visits	2700	27 visits	2700
Loss of income (£240 60/week)				
90 patients	30 days	92802·85	21 days	64962 00
10 patients	45 days	15467 14	45 days	15467 14
Average cost/patient		1539·7		2276 3

the wound is left open, but this is reduced to 27 days if the wound is partially closed by attaching skin edges to the presacral fascia (marsupialization).

Excision and primary closure

Excision of involved tissue followed by primary skin closure has the advantage, compared with healing by second intention, of quicker healing and greater convenience for the patient since prolonged open wound dressing is avoided. The disadvantage is that inpatient stay and general anaesthetic are usually necessary, and failure of primary healing may delay eventual healing by open granulation[32]. Primary healing was achieved within 2 weeks in over 90 per cent of the patients included in the studies in *Table 4*. Remaining patients require opening of all or a part of the wound with subsequent treatment, after a period of delay, by the open method.

Asymmetrical[117] or oblique elliptical[118] skin incisions have been advocated as an adjunct to primary closure in order to keep the incision away from the natal cleft and to flatten the natal cleft to reduce buttock friction. Results (*Table 5*) of these procedures suggest a healing time and failure rate (9 per cent) which are similar to those of primary closure.

Techniques involving skin flaps

The use of skin flaps to cover a sacral defect after wide excision has the advantage of keeping the scar away from the midline, and of flattening natal cleft contour, thereby reducing skin friction and accumulation of hair and debris[19] Complications are loss of skin sensation in the flap in 50 per cent of patients[125] and flap tip necrosis. Primary healing is achieved in 90 per cent of cases (*Table 6*). The disadvantages are that hospital admission and general anaesthesia are necessary, and the surgical technique is more demanding.

Should antibiotic prophylaxis accompany treatment?

Aerobic and/or anaerobic organisms are found in 50–70 per cent[115,137,138] of cases of pilonidal sinus. In one of the few randomized trials assessing treatment of pilonidal sinus, Kronborg *et al.*[96] found that clindamycin prophylaxis (chosen for effect against both anaerobes and *Staphylococcus aureus*) significantly reduced average healing time after primary closure Courtney and Merlin[116] have suggested that topical fusidic acid gel may be useful prior to primary closure, but controlled data are not available. Marks *et al.* reported[77] that healing after laying open of pilonidal sinuses was more rapid if a prophylactic 14-day course of oral metronidazole was given when patients were compared with a no prophylaxis, randomized, control group. This benefit could also be produced by treating with metronidazole only those patients whose granulating wounds appeared unhealthy

After care and local depilation

Irrespective of the method used, meticulous attention to hygiene and shaving of the surrounding area is essential to prevent penetration of the healing area by hair. The higher recurrence rate among poor clinic attenders[63] and variation in results after primary closure (*Table 4*) can probably be attributed to this. However continued depilation does not reduce local recurrence. Fifty years ago it was suggested[139,140] that low dose (<1000 cGy) skin irradiation produced a transient local depilation after pilonidal surgery which encouraged complete healing and reduced recurrence. Goodall[78] reported on a small group of patients in whom radiation depilation had been used but recurrence was not reduced. Much of the hair and debris that enters a pilonidal sinus is not locally derived and there is likely to be little advantage from local depilation in prevention of recurrence

Recurrence rate after treatment of pilonidal sinus

Recurrence increases with length of follow-up after treatment[16,141] but the majority occur within 3 years[16]. In addition, poor clinic attenders have more recurrence than those who attend regularly[63]. Thus studies with more complete and longer follow-up will tend to report a higher recurrence rate. Early recurrence after treatments which leave an open wound may be confused with incomplete healing, but is easily distinguished after primary closure where healing by primary intention should occur within 14 days. In *Table 7*, recurrence in the studies shown in previous tables has been assessed at minimum follow-up of <1 or >1 year using methods described above It can be seen that cumulative recurrence increases after 1 year irrespective of treatment method. Treatment involving wide excision with marsupialization, primary asymmetric closure or skin flaps are associated with a recurrence rate of less than 10 per cent at intervals of more than 1 year from treatment.

Conclusions about choice of treatment

The lack of rigorous trials, and differences both in eligibility criteria for different forms of treatment and in length of follow-up make comparison between results of different treatments unreliable. Nevertheless, certain guidelines do emerge.

Pilonidal abscess

Pilonidal abscess is associated with a high (40–60 per cent) risk of further symptoms if treated by simple incision and drainage. Many pilonidal sinuses might be prevented if pilonidal abscess were more effectively treated. This involves recognition and treatment[14] of the pilonidal pit as the underlying cause of the pilonidal disease either at the time of drainage or shortly thereafter. Some early pilonidal infections, associated with folliculitis in the absence of a foreign body granuloma, respond to antibiotic treatment and can be definitively treated once the oedema has settled

Closed techniques

Closed techniques based on brushing or phenolization of the track produce similar early results (*Table 1*) to those which involve laying the track open (*Table 2*). Both techniques require a 1–2 month period of careful shaving and lavage of the natal cleft, but in the former case the wound is smaller (absent with the phenol method) and prolonged open wound dressing is avoided Both techniques are suited to outpatient treatment using local anaesthetic However recurrence after 1 year is higher after these closed methods (*Table 7*), perhaps because natal cleft contour is not reduced (see below, Causes of recurrence).

Wide excision and healing by granulation

Wide excision of all tissue down to the sacrum leaving the wound open to granulate can never be justified. There is no theoretical or practical advantage, hospital admission and general anaesthetic are required, healing takes 2–3 months, and the recurrence rate after 1 year is similar to that after laying the track open. Marsupialization of the wound partially overcomes the difficulty of prolonged healing and is associated with a lower recurrence rate than after other open methods (*Table 7*). Although marsupialization usually requires hospital admission, it can be carried out under local anaesthetic and may have a particular role in management of the large pilonidal abscess[98].

Primary closure versus *laying open*

Excision with primary closure offers complete healing to most patients within 2 weeks. The proportion of patients who are unhealed at 2 months following primary closure[115] is similar to the proportion who remain unhealed 2 months after laying open[86]. It has been suggested that, if motivated, patients can return to work early after laying-open[77] However, primary closure allows an earlier return to work since many patients find it difficult to work with an open wound. In a study of motivated airforce personnel[105], return to work after laying open (mean 29·1 days) was longer than after primary closure (mean 21·7 days). In a population of civilians in London, Notaras reported[16] that average time off work after primary closure was 6 weeks compared with 7 weeks after laying open. Similar results have been reported from New Zealand[52]. The drawback of primary closure is that hospital admission and general anaesthetic are usually considered necessary and good results are surgeon dependent Primary healing rates tend to be higher in reports from a particular enthusiast[113,114] who is motivated to achieve the best possible result compared with reports of an overall general hospital experience[16,52] where the operation may be performed by surgeons who are less experienced in management by primary closure.

Relative treatment costs vary according to assumptions made about loss of income, and hospital and district nurse costs (*Table 8*). For most practical assumptions, treatment cost (hospital and district nurse cost, and loss of income) is 40–50 per cent higher for primary closure than for laying open (*Table 8*). A similar difference in treatment cost has been reported from New Zealand[52]. Although economy is the main advantage of laying open, reports[75] of treatment by laying open involving hospital admission for periods sufficient to achieve primary closure suggest that cost advantages of laying open are not fully exploited in the UK.

Primary closure with asymmetric incision or skin flap

Primary closure leaving a midline scar is associated with a cumulative >1 year recurrence rate (*Table 7*) of 18 per cent whereas recurrence rates approximate to less than 10 per cent after primary closure which displaces the scar from the midline. Of these two treatments, the asymmetric method of primary closure (*Tables 5* and *7*) is simple, has the same early success rate as primary closure but has the advantage of a lower recurrence rate. Although myocutaneous skin flaps also produce reliable healing with low recurrence (*Tables 6* and *7*), they require prolonged hospital admission, are more technically demanding and utilize more operating time than other treatments. Unlike other primary closure methods where failed healing can be treated by the open method, loss of all or part of a skin flap is a more serious complication.

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Causes of recurrence

The recurrence rate at 1 year following open methods of treatment (13 per cent) is less than after primary closure (15 per cent). Possible reasons for this are: (1) the midline scar is more susceptible to subsequent hair perforation than after healing by granulation; (2) the broader scar after healing by granulation reduces local hair growth; (3) there are fewer hair follicles near the midline to produce further folliculitis; and (4) the broader scar resulting from secondary healing flattens the natal cleft to reduce buttock friction.

It is unlikely that a scar produced by one method of healing should be intrinsically more vulnerable to hair penetration than another, and the reduction in local hair growth arising from healing by second intention is minimal. The low recurrence after skin flap procedures where hair follicles are present in the midline suggests that recurrent folliculitis is unlikely to be the reason for the difference. The most likely explanation is that healing by granulation, in particular after marsupialization where the natal cleft is distorted by suture of the skin edge to presacral fascia as well as by asymmetric and flap methods, alters the natal cleft contour thereby lessening both local accumulation of debris and buttock friction.

The aims of the ideal treatment for pilonidal sinus, namely reliable healing with low risk of recurrence, avoidance of hospital admission and general anaesthetic, and minimal patient inconvenience and time off work, could be achieved more frequently than at present. However no method satisfies all criteria. Scope for improvement using open methods of treatment seems limited because an open granulating wound inevitably means regular dressing over a period of weeks. Closed methods have a high risk of recurrence and healing takes as long as after laying open. Asymmetric primary closure appears most promising but requires hospital admission. There is now a need for randomized controlled trials comparing either laying open or one of the closed methods (*Table 1*) with asymmetric primary closure as a day case[121]. These studies should not only compare healing time but also recurrence rates at least 3 years after treatment, number of nurse and hospital visits, patient inconvenience and time off work. In development of new treatments the importance of reducing recurrence should not be overlooked in the drive for economy. The obvious ways of achieving this are by discouraging the two main causes of pilonidal disease, namely accumulation of hair and debris in the natal cleft, and buttock friction.

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Surgical workshop

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The Emeltract® mechanized surgical retractor

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Operative retraction can be provided by one of two methods, either the retractor is hand held or it is attached to a fixed but adjustable framework; neither is entirely satisfactory. Hand held retraction, while offering infinite variability, is limited by loss of concentration and fatigue in the assistant. Currently available fixed retractors[1,2] also have drawbacks. Although fatigue is not a problem there is an inherent restriction on the positions which can be achieved. The Emeltract Retractor® (Engineering in Medicine Ltd, London, UK) has been developed to provide both unwavering retraction and infinite adjustability.

The retractor comprises a ring with one or more carriages and a variety of blades (*Figure 1*). All the components are made of stainless steel and are readily autoclaved in the theatre suite. The ring is attached to the operating table by a single support which may be positioned to accommodate any operative field The retractor blade is mounted on a carriage, any number of which may then be located onto the ring (*Figure 2*). A combination of the circumferential movement of the carriage, a, on the ring, b, the rotational movements of the ball and socket, c, within the carriage and the pivotal movement of the top joint, d, allow the retractor blade to be placed in a wide variety of positions.

These features give The Emeltract four main advantages: it can be positioned by the operator using only one hand, the multiple degrees of freedom all lock with a single action; the wound edges can be lifted as well as retracted laterally; assembly and peroperative adjustment of the device can be effected easily and rapidly. A system is therefore provided which may be manipulated with the minimum of disturbance to the routine of the operation. The retractor has been designed primarily for use in abdominal surgery and its versatility has been verified in a number of operations carried out at The Middlesex Hospital including oesophagectomy, cholecystectomy and total colectomy. As a result of using the retractor we found that exposure of the operating field was improved and the risk of inadvertent tissue damage reduced. The Emeltract also allows assistants to be released from the tedium of retraction thereby making them available to help with more complex manoeuvres.

It is anticipated that the retractor in its present form will be used in thoracic, gynaecological and urological surgery; however future developments incorporating miniaturization will extend the range of its use to smaller operative fields such as are found in the head and neck.

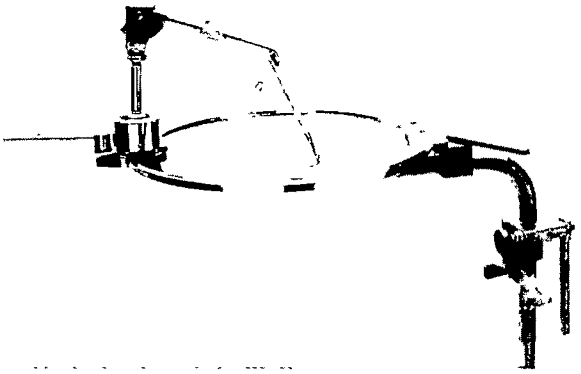

Figure 1 *The component parts of the Emeltract mechanized surgical retractor*

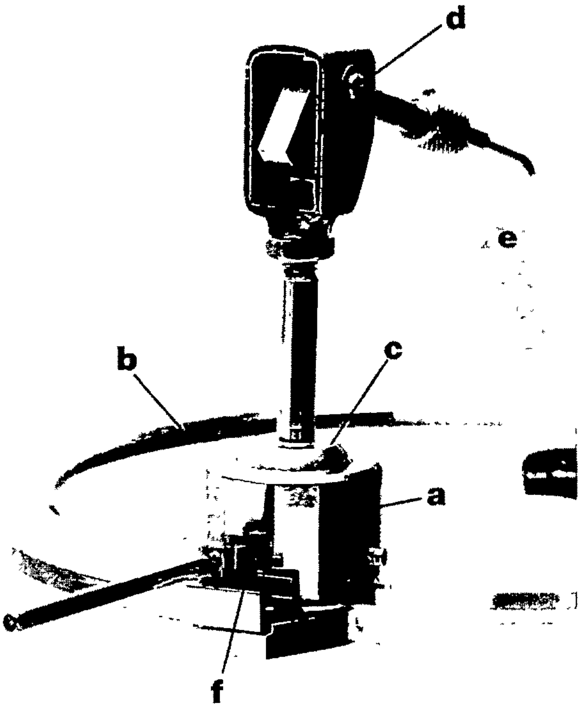

Figure 2 *The component parts of the carriage mechanism* **a**, *carriage*, **b**, *ring*, **c**, *ball and socket*, **d**, *top joint;* **e**, *blade*, **f**, *cam*

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Endoscopic transanal resection of rectal tumours – a preliminary report of its use

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Endoscopic transanal resection (ETAR) of rectal tumours is a simple and inexpensive procedure, well tolerated in elderly patients or those undergoing palliation. We have performed 137 ETARs in 81 patients with a 30-day mortality rate of 11·1 per cent and a postoperative complication rate of 15·3 per cent. Thirty-one patients (38 per cent) had ETAR for palliation: in this group rectal bleeding was abolished or improved in 66 per cent of patients, altered bowel habit (diarrhoea) corrected in 77 per cent of patients, faecal incontinence improved in 50 per cent of patients and rectal pain (including tenesmus) improved in 50 per cent of patients. Twenty-three patients (28 per cent) were treated for large benign rectal polyps: in this group symptoms were universally abolished. The technique is particularly suited to the management of these patients. Twenty-seven elderly patients with theoretically 'curable' rectal cancer underwent ETAR with a 78 per cent crude survival rate at 1 year. While long-term results remain to be assessed, ETAR appears a useful technique for treating selected patients with rectal tumours.

Keywords: Rectal tumours, palliation, endoscopic transanal resection

Malignant and benign rectal tumours are common in the UK Carcinoma of the rectum and some large villous adenomas are normally treated by anterior resection or abdominoperineal resection – major undertakings for elderly, frail patients and those receiving palliation alone[1]. In addition a colostomy is an unwelcome burden to the blind and to patients with a limited life expectancy. Alternative methods of treating these patients have been sought which avoid major abdominal surgery Palliation has been achieved with varying degrees of success by interstitial or external beam irradiation[2], electrocoagulation[3,4], chemotherapy[5], cryotherapy[6] and laser therapy[7]. Early cancers and benign rectal polyps can also be completely removed by transanal[8] or by trans-sphincteric excision[9]

Endoscopic transanal resection (ETAR) of rectal tumours has been described in a few patients using urological resectoscopes[10–13]; the largest series so far is of 23 patients[14]. We have studied the early results and morbidity from a large series of patients with benign and malignant rectal tumours.

Methods

The operative technique is very similar to transurethral resection of the prostate or of a bladder tumour A large diameter (36 Fr gauge) resectoscope is used which has a 20 cm sheath, a Blandy resectoscopic slide, appropriate cutting loops and a 30° fore oblique telescope (Genito-urinary Manufacturing Company, London, UK).

Patients are restricted to clear fluids by mouth for 24 h before surgery and a phosphate enema is administered before operation Two or more units of blood are cross-matched for patients with large tumours A single peroperative dose of cefuroxime 750 mg and metronidazole 500 mg is given intravenously If the resection extends into the perirectal fat the antibiotics are continued empirically for 5 days

The operation is performed under general or spinal anaesthetic with the patient in the Trendelenburg lithotomy position. The resectoscope is inserted through the anus and inspection or resection performed with continuous irrigation of 1·5 per cent glycine urological solution. Anal sphincter tone alone is sufficient to allow adequate rectal filling and continuous irrigation at low pressure, to minimize the risk of perforation and extravasation of the irrigating fluid when the rectal wall is breached. Resection is performed with a deep cutting loop for large tumours while a shallow loop is used for superficial lesions such as carpet-like villous adenomas. Resection usually begins at the lower, more accessible, edge of the tumour and from here the surgeon works cephalad and laterally removing as much of the tumour as possible Haemostasis can be achieved using a ball electrode The depth of resection can be judged by the appearance of the circular and longitudinal muscle fibres or perirectal fat which are readily differentiated from tumour Tumours may be seen invading muscle, fat, vessels or lymphatics in cords The potential limit of resection is dictated only by the length of the resectoscope, but clearly there is a risk of free perforation anteriorly and laterally above the peritoneal reflection. Throughout the resection the effluent irrigating fluid containing tumour fragments is funnelled into a urological collecting tray and retained for histological examination. Patients may require repeated resections to maintain an adequate lumen and decrease tumour mass

Results

Eighty-one patients with a mean age of 76·1 years have undergone a total of 137 ETARs. Fifty-two patients underwent a single procedure while the remaining 29 underwent multiple procedures (two in 14, three in seven, four in five, five in two and six in one patient). The diagnosis was adenocarcinoma of the rectum in 54 patients (68 per cent), tubulovillous adenoma in 23 patients (28 per cent), carcinoma of the prostate stenosing the rectum in three patients and in one patient the histology was non-diagnostic Thirty-one patients (38 per cent) with carcinoma (mean age 77·6 years) underwent the procedure for palliation alone, either because the lesion was disseminated or because the patient was considered too frail to withstand major surgery Of 27 patients with potentially curable rectal carcinoma, 21 (78 per cent) were alive after 1 year.

The distance of tumours from the anal margin and the length of tumours resected are shown in *Table 1*: 28 per cent of tumours

Table 1 *Characteristics of the tumours resected*

Distance from anal verge (cm)	1–5	6–10	11–15	>15
No	44 (54)	28 (35)	7 (9)	2 (2)
Length of tumour (cm)	1–2	3–5	6–10	>10
No	12 (15)	39 (48)	25 (31)	5 (6)
Quadrants involved	1	2	3	4
No.	19 (23)	24 (30)	22 (27)	16 (20)

Values in parantheses are percentages

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were judged clinically to be fixed at the time of operation and 20·5 per cent of patients had circumferential tumours.

The most common operative complication was haemorrhage which was severe enough to require blood transfusion and/or rectal packing in eight patients. Three patients suffered intraperitoneal perforation of the colon and underwent immediate laparotomy, two of whom died. Three other patients developed pelvic sepsis thought to be due to perforation beneath the pelvic peritoneal reflection. Two patients with large malignant tumours eventually developed rectovaginal fistulae after repeated resections. Other complications are shown in *Table 2*.

If two long-stay elderly patients are excluded, the mean length of postoperative stay in survivors was 5·9 days (range 1–23 days), and there was no difference between the length of stay after the initial or subsequent procedures.

There were nine postoperative deaths (30-day mortality rate 11·1 per cent) from 137 procedures (*Table 3*) One of these occurred in a patient with benign disease (patient no. 5), while four occurred in patients undergoing palliative procedures (nos. 6, 7, 8 and 9). Only four deaths (5 per cent) were attributable directly to complications of the procedure (nos. 2, 3, 7 and 9). Three patients died of chronic respiratory failure (nos. 1, 4 and 5) and two of disease progression (nos. 6 and 8).

The commonest presenting symptoms were rectal bleeding and change of bowel habit (usually diarrhoea) and these symptoms were abolished or improved in 83 per cent and 75 per cent of patients treated for cure respectively (*Table 4*). The symptoms of rectal pain (including tenesmus) and faecal incontinence were abolished or improved in 54 per cent and 60 per cent of patients respectively. In patients undergoing palliative surgery alone (*Table 5*) the incidence of pain and incontinence was higher but similar rates of symptomatic improvement occurred. Patients with benign polyps all achieved total relief or improvement of symptoms

Table 2 *Operative and postoperative complications (total 137 procedures)*

Complication	No. of patients (polyps)
Haemorrhage	8 (2)
Pelvic sepsis	3 (1)
Intraperitoneal perforation	3
Septicaemia	2
Rectovaginal fistula	2
Stricture/ulcer	2 (1)
Urinary retention	1 (1)
Total	21

Discussion

Endoscopic resection has an established history in urological surgery, curing patients with biologically favourable bladder tumours and palliating patients with aggressive lesions, as well as relieving bladder outflow obstruction in patients with prostatic malignancy. The technique has been used for endometrial ablation in dysfunctional uterine bleeding[15]. There is, therefore, an *a priori* case for using the same technique for rectal lesions

Patients with metastases, local incurable recurrence or potentially fatal medical conditions require relief of distressing symptoms of rectal tumours, if possible avoiding major surgery and a stoma. Radiotherapy produces both subjective and objective palliation[2] particularly if higher doses are used, but the response is slow, the technique is expensive and is not repeatable and the morbidity rate increases with dose Cryotherapy with liquid nitrogen produces more rapid tumour destruction and can be repeated[6], but is only applicable to very low tumours and has not been widely adopted Similarly, electrocoagulation or fulguration[3] may only be used for low rectal lesions Because these techniques require prolonged anal

Table 3 *Cause of death following ETAR (mortality 11·1 per cent)*

Patient no.	Age (years)	Diagnosis	Cause of death	Time of death (postoperative day)
1	78	Carcinoma	Myocardial infarction	9 (2nd ETAR)
2	77	Carcinoma	Perforation faecal peritonitis	<1 (2nd ETAR)
3	86	Carcinoma	Septicaemia	<1 (4th ETAR)
4	76	Carcinoma	Respiratory failure	23
5	86	Adenoma	Bronchopneumonia	22
6	63	Carcinoma (palliative)	Disease progression	26
7	57	Prostatic carcinoma (palliative)	Pelvic sepsis, ileus metastatic disease	13
8	79	Carcinoma (palliative)	Disease progression	26
9	77	Carcinoma (palliative)	Perforation, peritonitis	<1

Table 4 *Symptomatic relief in patients treated for cure*

Presenting symptoms	No. of patients	Symptoms abolished	Symptoms improved	No change	Not known
Bleeding	34	21 (62)	7 (21)	6 (18)	0
Change of bowel habit	28	12 (43)	9 (32)	2 (7)	5
Rectal pain (tenesmus)	13	3 (23)	4 (31)	3 (23)	3
Faecal incontinence	5	1 (20)	2 (40)	2 (40)	0
Prolapse	3	3	0	0	0
Pruritus	1	1	0	0	0

Values in parentheses are percentages

Table 5 *Symptomatic relief in patients undergoing palliative surgery*

Presenting symptoms	No of patients	Symptoms abolished	Symptoms improved	No change	Not known
Bleeding	12	4 (33)	4 (33)	1 (8)	3
Change of bowel habit	18	6 (33)	8 (44)	3 (17)	1
Rectal pain (tenesmus)	12	2 (17)	4 (33)	4 (33)	2
Faecal incontinence	6	1 (17)	2 (33)	3 (50)	0
Vaginal discharge (fistula)	1	0	0	1 (100)	0

Values in parentheses are percentages

dilatation for access, which may damage sphincters, they are usually reserved for small lesions

Early reports of endoscopic transanal resection in a few patients[10–14] suggested that the technique was effective and worthy of a more extensive trial because of its simplicity and repeatability. The success suggested by the earlier reports has been repeated in this study, particularly with tumours below the pelvic peritoneum. Resection of tumour as it extends through the rectal wall produces remarkably little morbidity but we feel it is prudent to continue antibiotics for 5 days when the perirectal tissues are opened The risks of peritoneal perforation increase with more proximal tumours and must be weighed against the symptoms to be palliated and the surgical alternatives.

Palliation of pain from pelvic infiltration is satisfactory in only 50 per cent of patients. This figure may be improved by combining external irradiation with ETAR, accepting that healing may be impaired. This was exemplified by one patient treated initially by interstitial irradiation who was left with a painful radionecrotic ulcer after palliative ETAR

The principal disadvantages of ETAR are that the patient requires general or spinal anaesthesia and must be relaxed, and that tumours above 20 cm are not accessible. Both of these disadvantages are overcome by the technique of laser therapy which has been used successfully to palliate patients with colorectal tumours[7]. However, laser therapy is slower than ETAR, the equipment is more expensive and is not yet freely available. Laser therapy can be performed under mild sedation as a day case but may have to be repeated at 3–4-weekly intervals compared with 3–4-monthly intervals for ETAR. Colonic perforation remains a potential risk with laser therapy as well as ETAR It is possible that both methods of treatment produce palliation by debulking tumour and retarding regrowth by scarring and fibrosis. A controlled comparative study of ETAR and laser therapy now appears appropriate and practicable.

Small, low, villous adenomas are easily excised transanally, but extensive lesions are difficult to treat and in the past have required difficult transanal excision[8], a parasacral approach[9], anterior resection or even abdominoperineal excision of the rectum. The high malignant potential of large villous adenomas and their potential to produce profound electrolyte disturbance from mucous diarrhoea have justified this radical approach. Large and extensive adenomas are relatively simple to excise with the resectoscope although several attempts are preferable and practicable. Re-epithelialization of the rectum with normal pliable mucosa is remarkably rapid even when large areas of muscularis are laid bare Other authors have recommended ETAR for patients with rectal villous adenomas[10,11] and it is our opinion that endoscopic resection is the method of choice for removing these tumours

Local removal of rectal cancers for cure, by any method, is controversial and is seldom used even though the overall results of radical surgery are often disappointing[16]. Conservative surgical techniques were first proposed in 1961 by Jackman[17] More recent reports of local techniques (including electrocoagulation through the dilated anus) have been published The tumour has to be at an early stage, <5 cm in diameter, protruberant and easily accessible[18–20]. Heat destruction of tumours appears to inhibit local recurrence, perhaps by producing an ischaemic scar and possibly by local cytotoxicity.

Transanal resection provides a simpler means of treating patients with favourable low rectal lesions and those who refuse to accept or are too frail to tolerate major surgery. While local recurrence may be more likely following ETAR, longer follow-up and actuarial analysis of the data are required to establish whether cancer mortality is different from patients receiving conventional surgical treatment. The operative mortality and morbidity is less than many reported series of major colorectal surgery in similarly aged and frail patients[21]. Endorectal ultrasound may be helpful in selecting suitable patients and in postoperative follow-up[22]

We conclude that ETAR is the method of choice for palliating patients with primary or recurrent rectal cancer and for treating patients with rectal villous adenomas It is also an acceptable method for treating patients with small, early, protruberant, mobile rectal cancers with the expectation of cure, and those with rectal cancers who are poor risks for major surgery.

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Short note

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Peroperative observation of marginal artery bleeding: a predictor of anastomotic leakage

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Anastomotic dehiscence following colorectal surgery is a major cause of postoperative mortality and morbidity[1–3], the reported incidence varies widely[4] but is frequently around 13 per cent for clinically diagnosed leaks[5,6] and much higher if dehiscence is sought radiologically[6]. Left-sided anastomoses are more prone to leakage than right-sided, and are more dependent for their integrity on the preoperative condition of the patient[7]. Many factors have been implicated in the failure of anastomotic healing but an adequate blood supply to the bowel ends is fundamental[1,2]. This in turn is influenced by the general circulatory status of the patient and the condition of the vessels themselves, deterioration in either will result in a reduction in blood flow to the anastomosis. A prospective study was undertaken to determine whether clinical measurement of blood flow in the marginal artery at operation might be a useful predictor of anastomotic healing

Patients and methods

Two hundred and seventy-five consecutive patients undergoing a left-sided colonic resection for malignant disease between 1975 and 1988 were included in the study One hundred and seventy patients underwent anterior resection, 62 sigmoid colectomy and 43 left hemicolectomy All patients had a primary anastomosis to the rectum or below

Patients who died within 14 days of the operation were excluded, with the exception of three patients in whom an anastomotic leak occurred prior to death. All patients underwent mechanical bowel preparation before operation

Blood flow to the anastomosis was assessed by transection of the marginal artery at the level of the proximal resection margin of the colon The observed blood flow from the cut end was recorded as pulsatile or non-pulsatile before ligation of the artery The anastomosis was performed using 3/0 Vicryl® (Ethicon Ltd, Edinburgh, UK) and a single layer inverting technique above the peritoneal reflection. below this level a staple gun was used Sixteen patients underwent coloanal anastomosis using a single layer of interrupted 3/0 Prolene® (Ethicon Ltd) sutures inserted from below

Anastomotic integrity was assessed radiologically by a water soluble single contrast medium examination[6] at 10 days, except in those patients who showed clinical evidence of a leak before this. Statistical analysis was performed on parametric variables using the χ^2 test, non-parametric variables were analysed using the Mann–Whitney *U* test for unpaired data.

Table 1 *Comparison of patients with pulsatile versus non-pulsatile flow from the marginal artery*

	Pulsatile ($n=195$)	Non-pulsatile ($n=80$)	*P*
Age at presentation*	67 (10·7)	67 (9·6)	≈1
Obstruction	20 (10)	6 (7·5)	0·6
Peritonitis	5 (3)	1 (1)	0·8
Poor bowel preparation	34 (17)	16 (20)	0·7
Palliative resection	35 (18)	12 (15)	0·7
Peroperative blood loss*	810 (601)	876 (540)	0·5
Peroperative blood transfusion*	877 (747)	1036 (693)	0·3

* Values are mean (standard deviation) Other figures in parentheses are percentages

Results

Non-pulsatile flow was observed in 80 patients: of these 15 (19 per cent) developed an anastomotic leak compared with 18 (9 per cent) of the 195 patients with a pulsatile flow ($P<0·05$); in three patients no flow was observed at operation and each sustained an anastomotic leak

No other significant differences were demonstrated between the groups of patients with pulsatile and non-pulsatile flow (*Table 1*). Altogether, 33 patients out of 275 (12 per cent) developed a leak from the anastomosis site after the operation. 28 had undergone anterior resection, with coloanal anastomosis in five of these patients The remaining leaks followed two left hemicolectomies and three sigmoid colectomies, all with an anastomosis to the upper rectum Seventeen leaks were diagnosed on clinical grounds: three patients succumbed to septic complications and one required formal closure of a rectovaginal fistula. The remainder settled on conservative management. Sixteen leaks were asymptomatic and were diagnosed on routine contrast medium studies or digital examination.

Discussion

The overall incidence of anastomotic leakage in this series was 12 per cent, with a clinical leak rate of 6 per cent This is comparable with most previously published rates[3,6], although twice that reported by Matheson *et al.*[8] using a single layer technique.

A comparison of the groups of patients showing pulsatile and non-pulsatile flow suggests that absent pulsatile flow in the marginal artery supplying the proximal limb of the anastomosis is associated with a higher incidence of postoperative dehiscence. Furthermore, anastomotic leakage occurred in all those with no observed flow from the marginal artery even though bleeding was observed from the cut end of the proximal bowel wall. Thus, a satisfactory assessment of the vascularity of the bowel wall alone (a good colour and fresh bleeding from

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the cut end) may not always indicate a blood supply sufficient for uncomplicated healing If bleeding from the marginal artery is also assessed and a pulsatile flow is present, the risk of anastomotic leakage should be reduced

The results of this study reflect the importance of a good blood supply in anastomotic healing but the relationship is probably not as simple as comparison of the two variables suggests. Flow in the marginal artery is a function of systemic as well as local factors, and these systemic factors are known to be labile in the perioperative period. Thus a non-pulsatile flow at the time of surgery is not necessarily an accurate reflection of inadequate postoperative perfusion, and it is not surprising that the majority of anastomoses in this group healed satisfactorily. Further resection of the bowel may achieve a pulsatile flow but this is not recommended if it results in an anastomosis under tension. In these patients a proximal stoma may lessen the sequelae of subsequent anastomotic leakage.

In summary, an observed pulsatile flow from the marginal artery at surgery was found to be associated with a lower incidence of anastomotic dehiscence: an absence of pulsatile flow does not, however, reliably predict an anastomosis at risk in the postoperative period.

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Case report

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Familial megaduodenum associated with hypoganglionosis

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Duodenal enlargement without evidence of obstruction is a rare finding[1], the term megaduodenum was used by Melchior in 1924 to describe such cases[2] We present a family unit in which the mother and two of her three siblings have the clinical and/or radiological features of megaduodenum. The familial nature and importance of adequate history taking and investigation in this condition are stressed.

Case report

The mother, a 39-year-old housewife, has a 30-year history of non-specific epigastric pain associated with nausea and anorexia Since 1973 she has complained of intermittent vomiting

She had numerous attendances at hospital but despite barium meal studies no diagnosis was made However, in 1978 a further barium study after an 8-year interval showed a grossly dilated atonic duodenum full of food residue A duodenojejunostomy provided symptomatic relief for 5 months. Subsequently (in 1983) she had a Roux-en-Y procedure using a wide duodenojejunal anastomosis at the lower pole of the second part of the duodenum in a further attempt to adequately drain the duodenum. Her symptoms were again initially relieved but have now returned to their presenting frequency and severity In addition the patient has now developed symptomatic reflux oesophagitis, unresponsive to medical management Her symptoms attributed to megaduodenum continue unabated; she remains underweight

The eldest son in the family, now aged 17 years, presented 5 years ago with epigastric pain and vomiting (frequency 2–3 times per month). A barium meal showed appearances similar to those of his mother Gastric emptying studies revealed 90 per cent retention of both liquid and solid contents of the test meal at 90 min From his original presentation his symptoms continued increasing in severity and frequency, but his weight and height remained above the 50th centile. Surgery was advised but was declined by the family until the patient was aged 17 years. At operation the duodenum was grossly dilated in its second and third parts. A retrocolic isoperistaltic duodenojejunostomy was performed in which the anastomosis was to the most dependent part of the duodenum at the junction of the second and third parts and was actually at the level of the sacral promontory. Full thickness biopsy of the duodenal wall demonstrated atrophy of the nerve plexuses. Cholinesterase staining confirmed the relative absence of ganglion cells and the sparsity of nerve endings in the submucosa. Jejunal biopsies were normal.

To date, 6 months after the operation, he remains asymptomatic However, postoperative barium studies (at 6 months) show a poorly emptying, grossly dilated, duodenum full of food residue (films taken after 12 h fasting, *Figure 1*).

The third affected member of the family is the youngest child, now aged 10 years He complained of non-specific abdominal pain, intermittent in character and usually occurring after eating. Radiologically he had a non-dilated, hypotonic duodenum. Delayed gastric emptying with retained gastric contents was clearly demonstrated Gastric emptying studies using a radioisotope technique showed initial delay in emptying but at 90 min 65 per cent of the test meal had emptied from the stomach.

Discussion

Various problems of gastrointestinal motility have been described in the literature. Isolated reports of non-familial adynamic bowel syndrome have been documented, in this syndrome the plexuses are normal macroscopically but deficient in acetylcholine[3,4]. In addition, some authors have described the syndrome of neuronal dysplasia occurring throughout the bowel although predominantly affecting the colon[5]. However, in this syndrome hyperplasia of the submucous and myenteric plexuses exist In neither of these syndromes is the histology similar to that which we have demonstrated. Nor have we detected any clinical abnormality of bowel motility distal to the ligament of Treitz on barium studies in our patients

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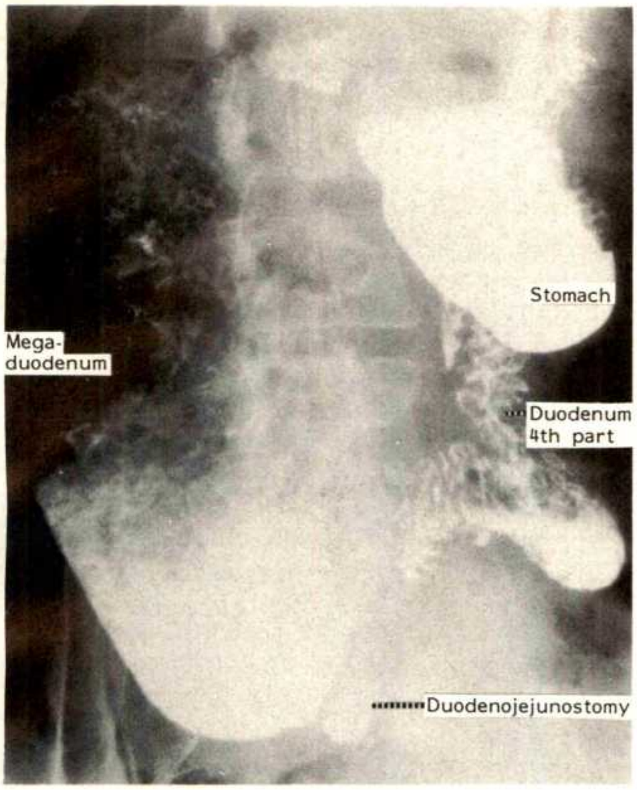

Figure 1 *Megaduodenum shown on a barium meal performed after a 12-h fast in 17-year-old son 6 months after operation*

Duodenal dilatation encountered in European clinical practice is most commonly related to mechanical obstruction. In one series six cases of aganglionosis of the duodenal myenteric plexuses with megaduodenum were presented; however, the familial nature was not a feature[6]. An association between megaduodenum and megacystis was reported by Law and Ten Eyck[7]. In their study nine members of the same family were affected, but histologically the duodenum was normal. Weiss[8] suggested a congenital aetiology when he reported megaduodenum and megacolon in several members of the same family. At operation megaduodenum with no evidence of mechanical obstruction was demonstrated but unfortunately no histological data are available. In their review, Barnett and Wall[6] describe epigastric discomfort as the most common symptom (74 per cent); vomiting occurred in 64 per cent and weight loss was present in 50 per cent of patients. No demonstrable physical signs occurred in 67 per cent of patients. The majority (71 per cent) of patients were diagnosed between the ages of 31 and 50 years. The definitive diagnostic test is the microscopic examination of a full thickness portion of the duodenal wall, revealing diminution in the components of the myenteric plexuses, particularly the ganglion cells. Histological examination as an aid to differentiation from Wilkie's syndrome is important.

Controversy exists regarding management. Law and Ten Eyck[7] suggest that many patients can cope with their symptoms and require no specific treatment. However, Newton[9] reports that the symptoms are progressive and that most patients require treatment. In one Brazilian series of 12 patients with Chagas' disease of the duodenum, duodenojejunostomy was satisfactory in eight patients but four required enterectomy[10]. At present most series favour using duodenojejunostomy initially, with the possibility of using an antral exclusion procedure for treatment failures. However, we suggest that early surgery before duodenal enlargement, hypotonicity and decompensation may yield better results.

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Blood transfusion and survival following surgery for prostatic carcinoma

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Blood transfusion in the perioperative period has been reported to have a detrimental effect on survival in many types of cancer. Other studies have failed to confirm this. We have examined retrospectively the records of 246 patients with prostatic carcinoma who underwent transurethral resection of the prostate (TURP) in Aberdeen Royal Infirmary between 1977 and 1982. Bilateral orchiectomy (BLO) was performed in 193 patients. Of these patients, 71 of 246 (29 per cent) received perioperative blood transfusion. After controlling for differences due to a number of variables, transfusion of non-autologous blood was shown to be associated with a significant negative effect on survival. Perioperative transfusion of non-autologous blood should be avoided in patients with malignancy, unless there are clear overriding clinical indications. Prospective trials are needed urgently.

Keywords: Blood transfusion, prostatic carcinoma, survival

It has become increasingly clear from recent studies that blood transfusion in the perioperative period is associated with an adverse effect on the survival of patients with a variety of tumours[1–10]. Time to recurrence of tumours may be shortened[1,11–13] and animal studies have suggested an increased risk of tumour metastases[14]. These effects are assumed to be related to immunosuppression associated with homologous blood transfusion, an effect which is now commonly used clinically to prolong renal allograft survival. The mechanism for this non-specific immunosuppression is the subject of a number of hypotheses[15,16]. The first was that this known immunosuppressive effect might be detrimental to patients with cancer who received transfusion[17], and the first report[18] in 1982 seemed to show a detrimental effect. However, some subsequent studies have given conflicting results[19–22] and the validity of comparing the immunosuppressive effect of blood transfusion in transplant patients and patients with cancer has been questioned[23].

Prostatic carcinoma may cause obstructive urinary symptoms requiring surgery, usually transurethral resection of the prostate (TURP). A common treatment for prostatic carcinoma is bilateral orchiectomy and, in Aberdeen Royal Infirmary, this was usually performed during the same hospital admission. Transfusion rates for transurethral prostatic surgery are relatively high. Previous figures in 162 patients with prostatic carcinoma (34 transfused, 128 not transfused) showed that the proportion of the transfused patients who had recurrences or died because of cancer was significantly higher than that of the non-transfused group[16]. The survival of 246 patients with prostatic carcinoma has been examined retrospectively to determine whether blood transfusion had a deleterious effect on survival and whether a change in transfusion practice in these patients should be considered.

Patients and methods

Using hospital computerized database records for the years 1977–1982 the names of all patients with a diagnosis of prostatic adenocarcinoma were retrieved. From operation codes, those patients who had been treated by transurethral resection of the prostate alone, or in combination with bilateral orchiectomy (BLO), were identified. There were 259 eligible patients during the years under study. Full records and follow-up information were complete for 246 of these. The records were examined and information obtained on age, date of operation, preoperative blood indices (haemoglobin, acid and alkaline phosphatase), TNM staging[24], histological grading, transfusion details and cause of death. The majority of operations were performed by two experienced urological surgeons.

Patients were considered to have had a transfusion if they had been given any blood product in the perioperative period 1 month before and after operation. Most transfusions were given in the immediate perioperative period. Details of whether whole blood, packed cells or other blood products were transfused were recorded.

Survival information was obtained from the hospital records or from the Primary Care Division of the Grampian Health Board which keeps a register of deaths in the region notified by general practitioners. Details of deaths of evaluable patients were collected up to 31 December 1987 – between 5 and 10 years after the patients' initial operation.

Statistical methods

Analysis was performed using the BMDP (1985) statistical software package (BMDP Statistical Software, Los Angeles, USA) on a Honeywell-Bull (San Diego, USA) mainframe computer. Programs used were BMDP1L (life tables and survival functions) and BMDP2L (survival analysis with covariates – Cox models). Patients were divided into transfused and non-transfused groups. The two groups were compared with regard to the individual covariates using χ^2 tests as appropriate. The cumulative survival rates were then calculated and life tables were constructed and tested using generalized Wilcoxon (Breslow) and generalized Savage (Mantel–Cox) tests. Multivariate regression analysis was performed using Cox's proportionate hazards models.

Results

Of the 246 patients, 221 had died by 31 December 1987 which was the end of the evaluable period. Of 71 patients transfused, 67 (94 per cent) had died, while in the non-transfused group, 154 (88 per cent) had died. The average amount transfused was 3 units, ranging from 1–11 units. The mean age at operation was 70·5 years. The two groups were comparable with respect to age, preoperative haemoglobin, type of operation, International Union against Cancer (UICC) staging and histological grade (*Table 1*).

As expected, there were differences in survival related to disease stage and histological grade. No difference was seen between those treated by TURP alone and those who had BLO too.

Kaplan–Meier life curves (*Figure 1*) were constructed for the two groups using the cumulative survival figures and showed a significant difference ($P < 0·0025$ using both Breslow and Mantel–Cox tests) between the two groups when all variables were taken into consideration. Kaplan–Meier life curves (*Figure 2*) were also constructed to compare patients transfused with packed cells and those transfused with whole blood. No

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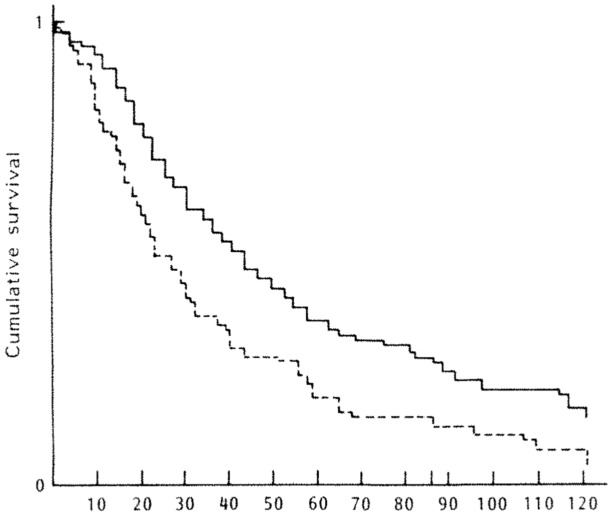
Table 1 *Characteristics of transfused and non-transfused groups*

	Non-transfused ($n=175$, 71%)	Transfused ($n=71$, 29%)	Significance
Mean age (years)	69·8(1·9)	72·0(1·1)	n.s.
Mean preoperative haemoglobin level (g/dl)	13·5(0·4)	12·2(0·4)	n.s.
Operation (%)			
TURP	20	19	n.s.
TURP+BLO	80	81	n.s.
UICC stage – 1T category (%)			
T1, 2 (combined)	60	65	n.s.
T3, 4 (combined)	41	35	n.s.
UICC stage – M category (%)			
M0	72	62	n.s.
M1	28	38	n.s.
Histological grading (degree of differentiation) (%)			
Well	54	42	n.s.
Moderately	12	14	n.s.
Poorly	34	44	n.s.

95% confidence limits given in brackets where appropriate. Differences between percentages tested using χ^2 test. n.s., not significant, $P>0·05$



No. surviving at 30, 60, 90 and 120 months

Transfused ($n=71$)	30	13	6	4
Non-transfused ($n=175$)	110	61	25	19

Figure 1 *Kaplan–Meier life tables of cumulative survival following surgery for prostatic carcinoma in transfused (– – – –) and non-transfused (——) patients. There is a significant difference between the two curves* ($P<0·0025$)

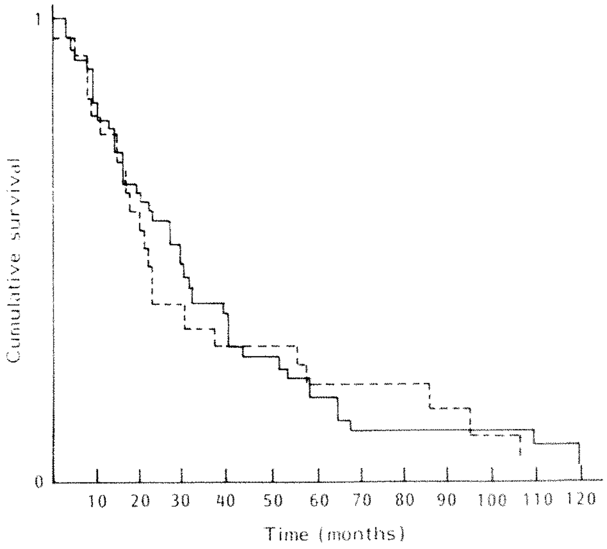
significant difference was seen between the two groups ($P>0·5$ using both Breslow and Mantel–Cox tests) but, as the numbers are small, this does not necessarily mean that the difference is negligible. The survival curves actually cross over at 40 months and this is not compatible with any great overall difference.

Proportional hazards regression analysis, using Cox's models, was then performed; when controlled for disease stage and histological grade only the variables age at operation (correlation coefficient/standard error = 3·5526, $P<0·00001$) and blood transfusion (correlation coefficient/standard error = 3·0458, $P<0·00001$) were found to have statistically significant effects on survival rates. It is of note that analysis of the deaths in the transfused group revealed that it was evenly distributed between deaths related to prostate cancer and deaths from other causes.

Discussion

This study was carried out using a large number of patients and there were a high number of deaths (statistical 'events'). The fact that this is a retrospective study, however, means that no firm conclusions as to causality can be drawn from these results. In addition, the methods used for grading and staging of prostatic tumours are a relatively inaccurate means of predicting the initial size or aggressiveness of the tumour. There may be subtle differences between tumours which may predispose to transfusion and are associated with a worse prognosis. An abnormal tumour vasculature may lead to excessive bleeding at operation, for example, and facilitate the early dissemination of metastatic tumour. A very significant difference between the two groups studied is demonstrated which cannot be explained by differences in tumour staging or other measured parameters. Retrospective studies on colonic, renal, breast and lung carcinoma have given conflicting results and it has been suggested that prospective studies are urgently needed to establish any possible causal relationship[25]. Compared with other groups, no difference in survival was demonstrated dependent upon the type of blood transfused.

The overall percentage of patients receiving a transfusion (29 per cent) reflects a range over the 5-year period studied from 40 per cent in 1977 to 22 per cent in 1982. This probably reflects improvements in both surgical instruments and anaesthetic techniques and is in keeping with recent figures (1987) of 28 per cent. This is a high rate of transfusion for transurethral prostatic surgery but it includes all perioperative transfusions and does not simply reflect transfusion rates at operation. The need for a prospective study is clear, but the method of carrying out such a study requires careful consideration. Preoperative anaemia, peroperative blood loss, operator skills, differences in clinical tumour staging, overall performance status of the patient and indications for transfusion are some of the factors requiring control in such a study. It would be an advantage to monitor the immunological status of patients before and after surgery (with or without associated blood transfusion). A careful history of both previous and any further transfusions would also be needed. There are also important ethical considerations to be taken into account before a controlled randomized trial could be carried out[25,26].



No. surviving at 30, 60, 90 and 120 months

Packed cells ($n=45$)	21	8	4	2
Whole blood ($n=26$)	9	5	3	1

Figure 2 *Kaplan–Meier life tables of cumulative survival following surgery for prostatic carcinoma in patients transfused with whole blood (——) and packed cells (– – – –). There is no significant difference between the two transfused groups* ($P>0·5$)

These results should lead to a further examination of present transfusion practices in patients with cancer. One of the reasons for preoperative transfusion, i.e. a low preoperative haemoglobin, has recently been questioned[27]. The use of autologous transfusion has been advocated for many reasons and, until prospective studies have been performed, should be considered, where feasible, in the patient with malignant disease having surgery. Blood loss has been shown to affect the outcome of metastatic growth[28] suggesting that even autologous transfusion in this group of patients may not be trouble-free. Rigorous criteria for transfusion should be established and adhered to until further studies have clarified these issues.

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Sutured posterior abdominal rectopexy with sigmoidectomy compared with Marlex® rectopexy for rectal prolapse

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Two treatment policies for rectal prolapse were prospectively assessed between April 1986 and January 1989. Sixteen patients had a Marlex® mesh posterior rectopexy alone and 13 underwent a sigmoidectomy combined with a sutured posterior rectopexy. Preoperative and post-operative assessment included manometry, a saline infusion test and video-proctography. Hospital stay, control of prolapse and complications were comparable in both groups. Restoration of continence occurred in nine of the 12 incontinent patients after Marlex rectopexy, compared with six of nine after sutured rectopexy and sigmoidectomy. Constipation persisted in three patients who were constipated before operation and in four of 13 who had previously normal bowel habits became constipated after Marlex rectopexy; constipation persisted in one of five previously constipated patients while none with previously normal bowel habits became constipated after sutured rectopexy and sigmoidectomy. Sigmoidectomy combined with sutured rectopexy was safe and as efficient as Marlex rectopexy in prolapse control and improvement of continence; significantly fewer patients were constipated (one of 13) after sigmoidectomy than following rectopexy alone (seven of 16). A randomized trial now seems justified.

Keywords: Rectal prolapse, constipation, incontinence, rectopexy, sigmoidectomy

Posterior abdominal rectopexy is regarded by many as the procedure of choice for the repair of rectal prolapse. Control of the prolapse is usually achieved in almost all patients in recently published series[1–4]. Residual disorders of defaecation, however, often follow successful prolapse operations. The main causes of patients' dissatisfaction are persistent incontinence and postoperative constipation. Approximately two-thirds of patients with a rectal prolapse accompanied by incontinence will regain continence by rectopexy alone[1–5]. However, some of these series also report that postoperative constipation is a troublesome functional disability[2,5].

Anterior resection of the rectum was proposed for the treatment of rectal prolapse by Muir[6]. This approach was later modified by authors who felt that a low pelvic anastomosis was not justified for a benign condition, and sigmoidectomy, sometimes combined with fixation of the rectal stump, was later performed[7–12]. Results of rectopexy and sigmoid resection (sometimes known as the Frykman–Goldberg operation) appear to equal those achieved by posterior abdominal rectopexy for control of the prolapse, but a detailed assessment of functional outcome is lacking. Nevertheless, constipation is claimed to be infrequent[9,12].

The present study was undertaken to evaluate prospectively the clinical and functional outcome of sutured rectopexy combined with sigmoidectomy, compared with posterior Marlex® (C.R. Bard Incorporated, Massachusetts, USA) abdominal rectopexy alone.

Patients and methods

Twenty-nine women were treated between April 1986 and January 1989 for a full-thickness rectal prolapse using one of two operations. Thirteen patients (median age 59 years, range 15–92 years) were treated by posterior sutured rectopexy combined with sigmoidectomy, and 16 patients (median age 57, range 22–79 years) underwent a posterior Marlex mesh rectopexy. Preoperative and postoperative evaluation included measurement of resting and squeeze anal pressures, a saline infusion test and video-proctography to measure the anorectal angle, anal canal length and rectal emptying, so as to observe the anatomical result of operation. Rectal emptying was assessed by introducing Baritop cellulose paste (Concept Pharmaceuticals, High Wycombe, UK) during proctography (120 G) and observing the amount evacuated in 1 min.

Operative technique

Posterior mobilization of the rectum with division of the lateral ligaments was identical in both groups. In the resection group the rectum was fixed to the presacral fascia with three non-absorbable sutures (Ethibond®, Ethicon, Edinburgh, UK) through the mesorectum; prosthetic material was not used. The sigmoid loop was resected without mobilization of the splenic flexure, and a one-layer hand-sutured colorectal anastomosis was fashioned between the descending colon and the upper rectum at the pelvic brim.

Marlex mesh rectopexy was undertaken as previously described[1].

Results

Anatomical control of the prolapse was achieved in all patients. The median hospital stay was 9 days (range 7–13 days) for patients having rectopexy alone and 11 days (range 8–14 days) in those whose rectopexy was combined with sigmoidectomy.

One patient developed a persistent small bowel obstruction requiring division of adhesions after rectopexy and resection, but no patients developed a leak or an abscess. There were two minor wound infections in each group.

Restoration of continence occurred in nine of 12 patients after rectopexy alone, and in six of nine patients who underwent additional resection. No patient was rendered incontinent by sigmoidectomy (*Table 1*). Constipation persisted in all three patients who were constipated before operation and four of 13 patients developed constipation for the first time after Marlex rectopexy. In contrast, preoperative constipation persisted in

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Table 1 *Functional outcome after surgery for rectal prolapse*

Preoperative status and outcome	Marlex rectopexy alone ($n = 16$)	Rectopexy with sigmoidectomy ($n = 13$)
Incontinent before operation	12	9
Unchanged or worse	3	3
Continence restored	9	6
Constipated before operation	3	5
Unchanged or worse	3	1
Constipation improved	0	4
Normal bowel habit before operation	13	8
Unchanged	9	8
Became constipated	4	0

Table 2 *Results of anorectal manometry before and after surgery for rectal prolapse*

	Resting anal pressure (cmH_2O)	Maximal squeeze pressure (cmH_2O)
Rectopexy with sigmoidectomy ($n = 11$)		
Preoperative	64 (50–116)	132 (92–327)
Postoperative	86 (50–135)	137 (50–305)
Marlex rectopexy alone ($n = 12$)		
Preoperative	52 (26–85)	122 (64–240)
Postoperative	69 (39–104)	134 (68–264)

Range is shown in parentheses

Table 3 *Rectal emptying following proctography in patients undergoing surgery for rectal prolapse*

	Rectopexy alone ($n = 16$)	Rectopexy with sigmoidectomy ($n = 13$)
Preoperative	82 (60–100)	74 (40–100)
Postoperative	*58 (0–84)	*41 (0–70)

* Statistical significance: $P = 0{\cdot}02$ (Wilcoxon test). Values expressed as median (range) percentage of contrast passed in 1 min after instillation of 120 G Baritop with cellulose into the rectum

only one of five patients and none developed constipation when rectopexy was combined with sigmoidectomy. There was no significant change in resting or squeeze anal canal pressures before and after operation in either group (*Table 2*). The volume at first leak during saline infusion was invariably less than 400 ml but did not change significantly after operation in either group. There was no significant difference in the videoproctographic variables before and after the operation in either operative group. However, after sigmoidectomy the rectum was continuous with the descending colon, whereas in the patients having rectopexy alone the sigmoid was invariably redundant and there was an acute angle between the fixed upper rectum and lower sigmoid. Rectal emptying was significantly decreased after operation in both groups (*Table 3*). There was no evidence of rectal stenosis at the site of rectopexy in any patient and recurrent intussusception was not observed.

Discussion

Two different operative treatment policies for rectal prolapse were prospectively evaluated in this study. The problem of anatomical correction of a rectal prolapse is now virtually solved by the various techniques of abdominal rectopexy which prevent further intussusception of the rectum. It was our intention, therefore, to study the effects of combining sigmoidectomy with posterior abdominal rectopexy as a means of improving functional outcome with particular reference to overcoming postoperative constipation.

Addition of resection and an anastomosis proved safe in this small series despite the fact that a high proportion of patients were elderly and frail. Control of the prolapse was achieved in all cases and the procedures proved equally efficient in improving continence. At follow-up, only one of 13 patients was constipated after resection and sigmoidectomy, compared with seven of 16 patients having conventional rectopexy alone: this was a statistically significant difference.

We recognize that this preliminary study will be criticized for not being a randomized trial but we felt constrained to ensure, in a pilot study, that addition of sigmoidectomy in this elderly population was safe and would not increase the risk of incontinence. There was no delibate selection process since we used a consecutive series of patients for sigmoidectomy. The age and incidence of incontinence were similar, but five of 13 patients having resection were constipated before operation compared with three of 16 before Marlex rectopexy.

Rectal emptying decreased significantly in both groups, suggesting that the process of rectal mobilization which was common to both groups might be responsible for impaired propulsive activity of the rectum. Division of the lateral ligaments and posterior mobilization is likely to interrupt some of the autonomic innervation of the rectum. This phenomenon might explain why some patients become constipated after rectopexy. In the Ripstein operation, rectal stenosis at the site of rectopexy might be responsible for constipation[13], but there was no evidence of stenosis during postoperative videoproctography in any of these patients. Furthermore, Marlex is used merely to stabilize the presacral sutures, and only the posterolateral aspect of the rectum is attached to the foreign material. In our opinion, development of constipation is much more likely to be due to a kinked and redundant sigmoid loop which forms an acute angulation deformity above the rectal fixation. Some patients with a rectal prolapse are severely constipated before operation, but they are a younger group and in some of them the prolapse may be a secondary phenomenon. Most of these patients have delayed colonic transit and it is possible that sigmoidectomy alone may be an inadequate resection. Only five of our 13 patients fell into this category and one of them has persistent constipation. We do, however, accept that the duration of follow-up is short and the long-term results, even of subtotal colectomy, in this group are frequently far from perfect[14].

Another interesting observation is that continence was not apparently impaired by sigmoidectomy, even in the elderly. Furthermore, as already observed[14], sutured posterior rectopexy appears to be just as effective in achieving posterior rectal fixation as insertion of a foreign body such as polypropylene mesh.

This pilot study suggests that a prospective, randomized, study would be justified, particularly as adjuvant postanal repair in patients with incontinence who have poor predictive parameters[5] (low pressures, short anal canal, perineal descent and an obtuse anorectal angle) seems unlikely to restore continence, and since persistent incontinence was no more frequent when sigmoidectomy was added to conventional rectopexy (three of nine cases compared with three of 12 cases, respectively). In any future study, it might be prudent to stratify patients into one of four groups with potentially different outcomes, namely: patients with secondary prolapse having prolonged colonic transit, those without incontinence and constipation, those with incontinence and good predictive parameters, and those with incontinence in whom the prospect of restoring continence seems dismal.

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Results of surgical treatment of neonatal necrotizing enterocolitis

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In 6 years, 74 neonates were treated for necrotizing enterocolitis, 40 (54 per cent) of whom underwent operation. The early postoperative mortality rate was 23 per cent and there was one late death. Of the 30 postoperative survivors, two have short bowel syndrome, two have chronic respiratory disease, two are partially sighted, and five (17 per cent) have severe developmental delay. Only 15 (50 per cent) survivors enjoy good health.

Keywords: Necrotizing enterocolitis, neonates, surgery

Since the syndrome of 'necrotizing enterocolitis' was recognized in the early 1960s[1], numerous authors have written about it, their papers being concerned with aetiological hypotheses, aspects of medical and surgical treatment, and short term outcome, but few papers have been concerned with the long term results in those surviving surgical treatment. The long term outcome of surgery needs to be known because necrotizing enterocolitis is said to be the commonest acquired gastrointestinal emergency in the neonatal intensive care unit.

Patients and methods

No babies are born in the Queen Elizabeth Hospital for Children, but neonates with necrotizing enterocolitis requiring prolonged parenteral nutrition, ventilatory support or surgical intervention are referred from a wide area of south-east England. Patients undergoing initial surgery elsewhere and only secondary procedures at this hospital were excluded from this series, as were those developing necrotizing enterocolitis after surgery for other conditions.

Between July 1980 and June 1986, 30 girls and 44 boys with necrotizing enterocolitis were referred for primary treatment. Medical treatment alone was sufficient for 28 infants, all of whom recovered and went home. This group of infants generally had relatively mild disease without perforation or stricture formation and all recovered without early complications. The majority were returned to the referring hospital for review and they will not be discussed further in this paper.

More serious disease was present in 46 infants, six of whom were moribund on admission and died before operation could be performed. Laparotomy was performed in 40 infants and they form the material of this paper. Antenatal problems (*Table 1*) and 'perinatal stress' (*Table 2*) were common in this group. All operations were performed or supervised by a consultant paediatric surgeon and consultant paediatric anaesthetist. Free intestinal perforation (55 per cent) was the main indication for operation (*Table 3*). Most patients in this group underwent laparotomy within 24 h of admission after receiving intensive medical treatment including fluid replacement, broad spectrum antibiotics and control of ventilation to improve peripheral circulation and the results of blood gas analysis. Extensive disease was found in the majority (*Table 4*). The distal ileum and caecum and the distal colon were the areas most commonly involved. Various surgical procedures were performed (*Table 5*) but in the majority (23 infants), the necrotic bowel was resected, and the proximal end was brought out as an enterostomy and the distal end as a separate mucous fistula. In the survivors, intestinal continuity was restored at a second operation once the acute phase had resolved.

Results

Early postoperative death occurred in nine infants; from sepsis and severe necrotizing enterocolitis in seven, from metastatic brain abscess in one and from pneumonia in another. Neither birth weight nor gestational age had any bearing upon survival but 'small for dates' babies weighing 2000-2500 g did badly. Thirty-one infants survived the initial admission but there was one late death. This infant had suffered prenatal growth retardation and required artificial ventilation from birth for idiopathic respiratory distress syndrome complicated by perforating gastric necrotizing enterocolitis. At the age of 1 month, pyloromyotomy was required for hypertrophic pyloric stenosis and computed tomographic scan revealed mild hydrocephalus and polyporencephaly. Recurrent respiratory arrests and convulsions led to death 1 month after discharge from our care.

The 30 survivors were followed for between 2 and 7 years. Severe mental retardation and motor delay were detected in five children of whom one has Klinefelter's syndrome, one has multiple abnormalities (including hydrocephalus, absence of the

Table 1 *Obstetric complications of the mothers of 36 of the 40 infants undergoing operation*

Complication	Number
Intrauterine growth retardation	8
Premature rupture of membranes	7
Premature labour	6
Pre-eclamptic toxaemia	8
Diabetes mellitus	2
Multiple pregnancy	2
Antenatal bleeding	7
Severe fetal distress	4
Other obstetric complications: each occurring in only one pregnancy	10
Normal pregnancy	5

No information was available in four cases, and some pregnancies had more than one complication

Table 2 *Early perinatal abnormalities and procedures in the 40 neonates undergoing operation*

Abnormality	Number
Respiratory distress requiring treatment	25
Umbilical vessel catheter	7
Exchange transfusion	2
Polycythaemia	2
Others	14
No identified problems	5

Some neonates had several problems

Table 3 *Indications for surgery for the 40 neonates undergoing operation*

Indication for surgery	Number
Freely perforated bowel/pneumoperitoneum	22
Deterioration despite intensive medical treatment	8
Intestinal obstruction	5
Extensive, severe necrotizing enterocolitis	2
Erroneous diagnosis of a different surgical problem	3

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Table 4 *The anatomical sites of necrotizing enterocolitis in the 40 neonates undergoing operation*

Anatomical site	Number
Stomach	3
Duodenum	5
Jejunum	9
Ileum	26
Caecum and ascending colon	23
Transverse colon	22
Descending colon	25
Sigmoid colon	24
Rectum	8

Only one patient had isolated involvement of the stomach

Table 5 *The various initial operative procedures performed*

Procedure	Number
Resection of necrotic bowel and exteriorization of the ends	23
Resection of necrotic bowel and primary anastomosis of the viable bowel	12
Exteriorization of the bowel without initial resection	2
Defunctioning jejunostomy	1
Drainage under local anaesthetic	1
Laparotomy alone, necrosis of the entire gastrointestinal tract	1

corpus callosum, cataract of the right eye, bifid thumbs and spastic diplegia), and one has been abandoned by his parents. Of the remaining 25, one has mild to moderate physical handicap from cerebral palsy, two have severe visual handicap (one from retrolental fibroplasia and one from cataracts), two have severe symptomatic bronchopulmonary dysplasia, two have growth retardation from short bowel syndrome and two have chronic diarrhoea (one of whom has severe iron deficiency anaemia unresponsive to oral therapy). Only 15 (38 per cent of those undergoing operation and 50 per cent of those surviving) are in good health.

Discussion

Early death occurred in 20 per cent of our patients and the initial postoperative mortality rate was 23 per cent. Overall initial survival rates of 75–80 per cent are now common[2-4], but extensive disease is associated with a mortality rate in excess of 95 per cent[5]. As in other series[2,4,5], poor prognostic features included persistent acidosis, thrombocytopenia, oliguria, and the presence of other congenital defects. Like Dykes *et al.*[2], we found birth weight and gestational age to be of little importance in prognosis, although some authors[5,6] have found a poor prognosis in infants of less than 28 weeks' gestation, or with a birth weight below 1500 g.

Most infants surviving necrotizing enterocolitis go through a recovery phase of temporary feeding difficulty with diarrhoea[4,7] but those without short bowel syndrome have normal growth at the age of 1 year[7]. The short-term effects of massive bowel resection are well known[8]. An ileocaecal resection leaving less than 40 cm of small bowel conveys a poor prognosis. Short bowel syndrome is associated with hyponatraemia, hypokalaemic acidosis, deficiency of fat soluble vitamins and bacterial overgrowth, resulting in hypomagnesaemia, hypocalcaemia, rickets and vitamin B_{12} and folate deficiency anaemia. The latter deficiencies may result in late neurological degeneration compounded by vitamin E deficiency[9]. Late problems may include night blindness from vitamin A deficiency, osteomalacia beginning after the adolescent growth spurt, gallstones and oxalate renal stones[10]. Fortunately, the small bowel has a remarkable capacity to adapt, allowing sufficient growth for most survivors to be of normal height and weight[11,12], but undernutrition in infancy may cause variable long term intellectual impairment[13,14] accompanied by perceptuomotor defects. Many survivors have abnormal results in psychometric tests[15]. Some of these problems may be avoided by early parenteral nutrition.

Few studies are available on the long term prognosis of infants surviving necrotizing enterocolitis. Abbasi *et al.*[7] studied infants, all but four treated medically, at 1 year of age and found that the majority with less than 25 per cent gut resection were biochemically normal although three of their 22 patients had severe neurological disabilities, as did two of the 18 controls without necrotizing enterocolitis. Whiteman *et al.*[16] studied 19 survivors of necrotizing enterocolitis and compared them with premature infants without non-necrotizing enterocolitis. They found that although those surviving necrotizing enterocolitis tended to be about the tenth centile for height and weight, those having surgery did less well than those treated medically. Stevenson *et al.*[17] were among the first to report on late morbidity in the survivors and found that half their patients were normal, 10 per cent had gastrointestinal impairment, and 15 per cent had severe central nervous system impairment. These results are similar to ours and those of several authors reporting series of patients treated either medically or surgically[4,18,19]. Intellectual impairment or developmental delay occurred in a third of the survivors of surgical treatment in the series of 63 infants reported by Cikrit *et al.*[20] and 17 per cent had seizures. Intraventricular haemorrhage is the most common finding in the brain of babies dying during the first week of life[21] and was considered to be one of the most important lesions responsible for handicap in surviving infants. For many years the association between intracranial haemorrhage and gastric perforation has been known[22,23] and an appreciable number of infants with necrotizing enterocolitis has intracranial haemorrhage. However, in this retrospective series, we were unable to find any factor that was statistically different between those survivors having a good and a bad prognosis with regard to late intellectual and motor development. Recent studies seem to indicate that postnatal periventricular haemorrhage may not be an important cause of developmental delay[24,25], although there seems to be no doubt that prenatal periventricular haemorrhage and leukomalacia are associated with severe mental retardation[26].

Except for neonates with multiple serious congenital anomalies, we are presently committed to aggressive treatment in every individual but this situation might not appertain if fetuses with leukomalacia and increased risk of severe mental retardation could be reliably detected before they became neonates with severe necrotizing enterocolitis. Prenatal growth retardation had been detected in 8 patients in our series and Doppler studies of the fetal aorta may be capable of predicting those growth retarded individuals at high risk of developing neonatal necrotizing enterocolitis, so allowing early delivery and prophylactic treatment[27,28].

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Metabolism of body water and electrolytes after surgery for ulcerative colitis: conventional ileostomy *versus* J pouch

Some authorities believe that patients with conventional ileostomies are chronically water and salt depleted but there are no data on the metabolism of body water and electrolytes after ileoanal J pouch. To clarify the situation we studied the body composition of 14 patients with well functioning ileostomies and 20 patients with well functioning J pouches. Both groups were compared with two closely matched control groups. Body weight, total body fat, fat-free mass, total body water and extracellular water were measured by neutron activation analysis, tritiated water and bromide dilution respectively; 24-h collections of urine and stool were analysed for volume and electrolyte content. The results show that the body content of water and extracellular fluid in ileostomy patients and J pouch patients is normal. The faecal volume and chemistry is similar in both groups resulting in a similar and significant degree of urinary sodium retention.

Keywords: Ulcerative colitis, ileostomy, ileoanal J pouch

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Ileoanal J pouch is an acceptable alternative to conventional ileostomy in patients who require surgery for ulcerative colitis[1]. It has long been held that conventional ileostomy is associated with chronic water and salt depletion[2] but it is not known if ileoanal J pouch is associated with similar problems. Because of this and also because there is some controversy over the fluid and electrolyte status of ileostomy patients[3,4], we measured body fluid compartments in a group of ileostomy patients and in a group of J pouch patients and compared the results obtained with their closely matched controls.

Patients and methods

Patients

All patients in the study had had surgery for ulcerative colitis. Fourteen patients with well functioning conventional ileostomies (ileostomy bag emptied 3–5 times/day; none on medication) together with 20 patients with well functioning J pouches (mean(s.d.) frequency of bowel movement 4·3 (1·4)/day; 12 patients on no medication, eight patients taking loperamide in mean (s.d.) dose of 4 (2) mg/day) were studied as outpatients together with their two closely matched control groups. Signed consent was obtained and the study had ethical approval from the Auckland Hospital Ethical Committee.

The ileostomy patients had had their procedure on average 14 years (range 1·5–30 years) previously. The 20 J pouch patients were all patients in G.L.H.'s series[5]; their loop ileostomies had been closed on average 18 months (range 6–40 months) before this study. Data relating to ileal resection were not available for the ileostomy patients. None of the J pouch patients had had an ileal resection.

Controls

To allow close matching of our two patient groups for age, sex, weight and height, two separate control groups were recruited. Normal volunteers were mainly recruited from either hospital personnel or their friends and families. In all cases the volunteers reported no ill health, were on no medications and were considered healthy.

Body composition

Basic body habitus measurements including body weight and height were performed.

Body composition measurements were carried out by a technique that has been previously described[6]. This included measurements of the total body protein by prompt γ *in vivo* neutron activation analysis in conjunction with measurements of total body water (TBW) by tritium dilution after an intravenous injection of 100 μCi tritiated water. The fat-free mass (FFM) was derived by adding body protein and total body water together with an estimate of total body minerals and glycogen[6]. In the case of minerals and glycogen, these were assumed to be linearly related to skeletal size according to regression equations derived from normals[7]. The precision of these measurements has been described elsewhere[8]. It is possible to estimate total body protein with a precision (standard deviation) of 4·2 per cent, total body water to 1·5 per cent and total body fat to 6·3 per cent. Fat-free body mass (FFM) can be estimated to within 1·6 per cent (most of the error is due to the error involved in tritium dilution, since 70 per cent of the fat-free mass is water)[8].

The extracellular water volume (ECW) was measured by bromide dilution[9], 50 ml of a 5 per cent sodium bromide solution being infused slowly over a 5-min period after a background sample of intravenous blood had been taken. An estimate of the bromide space was performed on a 10 ml sample taken from the contralateral arm 3 h after injection. The method of quantification relies on an easy colorimetric test following complexing with gold salts (intra- and inter-assay variation using this technique has been reported as <5 per cent; correlation coefficient $= 0{\cdot}995$)[10].

Urine and stool analysis

All patients and controls underwent 48-h collection of urine for volume and sodium and potassium content. The content of sodium and potassium was determined by a Conning flame photometer.

The patients collected 48-h collections of stool for analysis for volume and sodium and potassium content. A sub-sample of stool was homogenized and centrifuged and the supernatant was analysed by flame photometry to provide a measurement of the sodium and potassium content.

Statistical analysis

Quantitative data of the patient and control groups were compared using Student's *t* test. The fluid spaces were plotted against fat-free body mass and the results were compared by linear regression analysis.

Results

Table 1 shows the clinical details of the two patient groups and their respective control groups. The controls for the ileostomy group and the J pouch were not significantly different from their patient groups for age, sex, height and weight.

In *Figures 1* and *2*, total body water is plotted against the fat-free body mass for ileostomy patients and the J pouch patients respectively. These plots are compared with those of

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Table 1 *Clinical details of study groups*

	Control ($n = 14$)	Ileostomy ($n = 14$)	Control ($n = 20$)	J pouch ($n = 20$)
Male:female	6:8	6:8	11:9	11:9
Mean(s.d.) age (years)	45 (13)	44 (12)	35 (11)	33 (11)
Age range (years)	27–66	26–76	22–60	16–53
Mean(s.d.) body weight (kg)	68 (7)	63 (10)	71 (11)	68 (7)
Weight range (kg)	63–76	51–87	52–97	48–101
Mean(s.d.) height (cm)	169 (8)	168 (8)	174 (8)	169 (10)
Height range (cm)	157–183	156–186	159–193	153–186

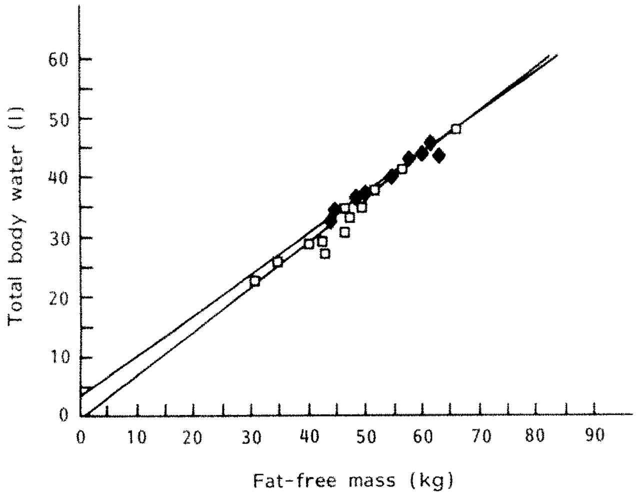

Figure 1 *Relationships between total body water (TBW) and fat-free mass (FFM) in ileostomy patients (□) and their controls (◆). Control TBW = 0·68 FFM + 2·96 (s.e.e. = 0·93, r = 0·98); ileostomy TBW = 0·73 FFM − 0·81 (s.e.e. = 1.43, r = 0·98)*

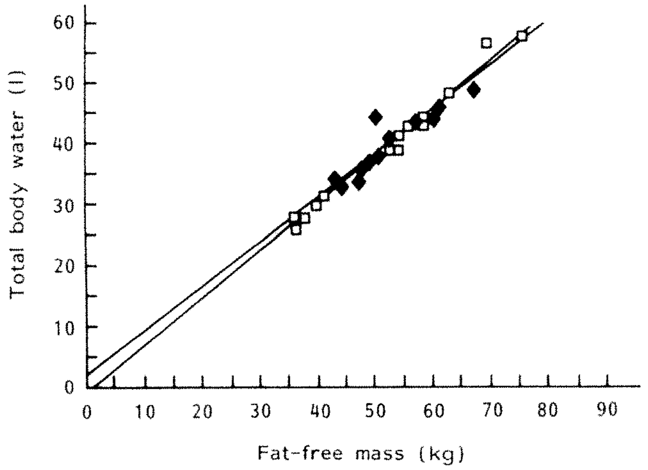

Figure 2 *Relationships between total body water (TBW) amd fat-free mass (FFM) for J pouch patients (□) and their controls (◆). Control TBW = 0·72 FFM + 1·50 (s.e.e. = 1·84, r = 0·98); pouch TBW = 0·76 FFM − 1·17 (s.e.e. = 1.13, r = 0·99)*

their control groups. It can be seen that the regression lines are almost identical for the patients and controls suggesting that chronic dehydration is not present in either patient group.

In our laboratory we have shown the mean(s.d.) normal hydration coefficient of the FFM is 72·6 (1·5) per cent for women and 71·1 (1·2) per cent for men[7]. In the present study the average(s.d.) hydration coefficient for all the female controls was 74·1 (2·5) per cent and for the male controls it was 72·7 (2·5) per cent. These values are not significantly different from the normal data.

In *Figures 3* and *4* extracellular water is plotted against fat-free body mass for the ileostomy patients and J pouch patients respectively, and these plots are compared with those of their control groups. The regression lines are similar for each patient group and their control group, suggesting that ileostomy patients and J pouch patients are not depleted of extracellular water.

The results of the 24-h faecal volume and 24-h faecal excretion of sodium and potassium are shown in *Table 2* together with the results of the 24-h urine volume and 24-h urine excretion of sodium and potassium in the two patient groups. It can be seen that there is no significant difference in

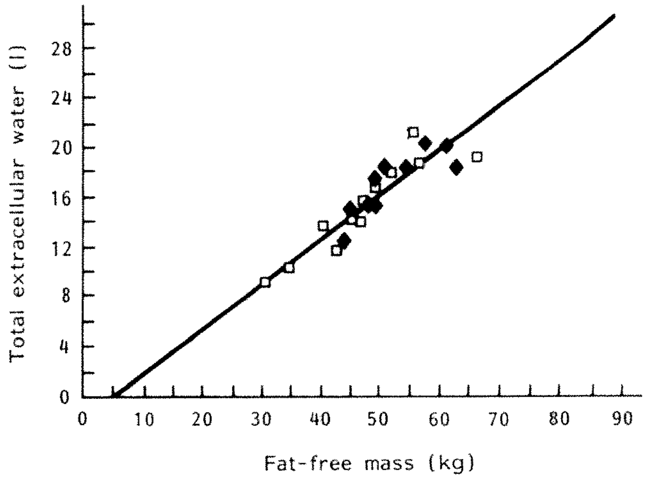

Figure 3 *Relationships between total extracellular water (ECW) and fat-free mass (FFM) for ileostomy patients (□) and their controls (◆). Control ECW = 0·36 FFM − 2·21 (s.e.e. = 1·50, r = 0·89); ileostomy ECW = 0·35 FFM − 1·95 (s.e.e. = 1·50, r = 0·91)*

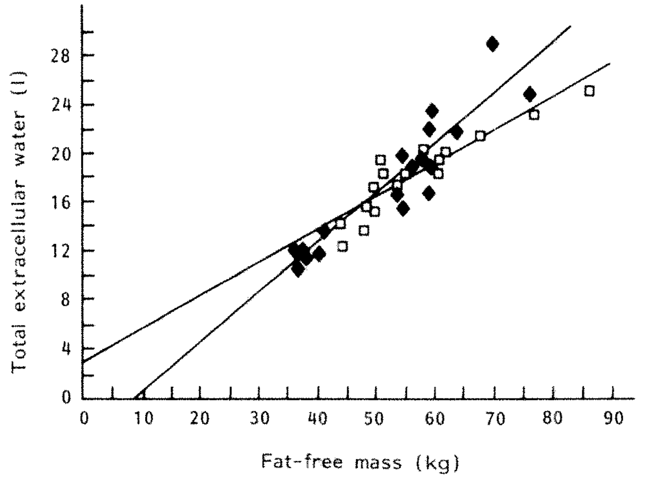

Figure 4 *Relationships between total extracellular water (ECW) and fat-free mass (FFM) for J pouch patients (□) and their controls (◆). Control ECW = 0·27 FFM + 2·93 (s.e.e. = 1·29, r = 0·92); pouch ECW = 0·40 FFM − 3·72 (s.e.e. = 1·83, r = 0·94)*

Table 2 *24-h faecal and urinary analysis*

	24-h stool analysis			24-h urine analysis	
	Weight (g)	Na (mmol)	K (mmol)	Volume (ml)	Na:K
Ileostomy	548 (40)	74 (10)	14 (5)	1171 (130)	0·96 (0·15)
J pouch	507 (9)	58 (10)	8 (1)	1139 (95)	1·17 (0·13)
P	n.s.	n.s.	n.s.	n.s.	n.s.

Values are mean (s.e.m.); n.s., not significant; *P* values calculated by unpaired Student's *t* test

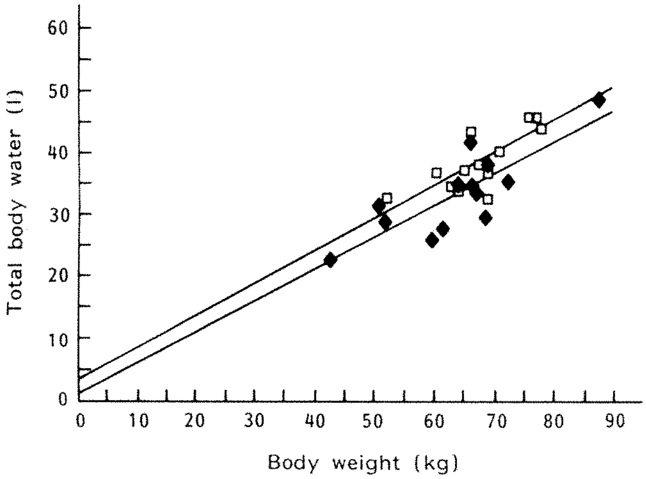

Figure 5 *Relationships between total body water (TBW) and body weight (BW) for ileostomy patients* (□) *and their controls* (◆). *Control* $TBW=0\cdot52\ BW+3\cdot04$ (*s.e.e.*$=3\cdot11$, $r=0\cdot79$); *ileostomy* $TBW=0\cdot50\ BW+0\cdot89$ (*s.e.e.*$=4\cdot00$, $r=0\cdot82$)

either the volume of stool or urine, or the electrolyte content of the stool or urine, between the ileostomy and J pouch patients. Although the controls appeared to have a higher daily urine output (mean(s.d.): 1554(100) ml), this was not significantly different from that of the ileostomy or the J pouch patients. The mean(s.d.) sodium:potassium ratio in the urine of the controls was 2·1 (0·3) and this was statistically higher ($P<0\cdot01$) than that for either the ileostomy or J pouch groups. There was, therefore, significant urinary sodium retention in both patient groups.

Discussion

There is no evidence in this study that patients with either conventional ileostomy or ileoanal J pouch are chronically water or salt depleted. Although the faecal outputs of water and sodium are similar after these procedures, they are 2–3 times higher than those of normal subjects. For this reason urinary conservation of water and sodium is to be expected but clearly the patients are compensating well and there are no whole body deficits.

These results are somewhat different from those described by Clarke *et al.* who interpreted their findings in a group of patients with well functioning ileostomies as showing a deficit of total body water[2] as well as a deficit of total exchangeable sodium[2]. Their findings, based on body weight rather than fat-free body mass, could be explained if their ileostomy patients had greater fat stores than their matched controls.

This possibility has been tested in our own subjects by directly measuring the fat stores (i.e. percentage of body weight that was fat) in both patient groups and controls. Both ileostomy and J pouch patients had significantly increased fat stores compared with their controls: mean(s.e.m.) of 27·3 (2·3) per cent in ileostomy patients *versus* 22·4 (1·5) per cent in controls ($P<0\cdot05$) and 26·0 (1·7) per cent in J pouch patients *versus* 19·9 (1·0) per cent in controls ($P<0\cdot005$). Furthermore, if our ileostomy data are plotted against body weight (*Figure 5*) as was done by Clarke *et al.* we show, like them, a similar (but erroneous) deficit in total body water of 9 per cent.

On the other hand our results are in agreement with more recent work, particularly that of Cooper *et al.*[3] and Turnberg *et al.*[4]. With regard to our finding of increased fat stores, this has not been a consistent feature in the literature and certainly Cooper *et al.*[3] showed that the amount of total body fat in their group of ileostomy patients, who had not undergone an ileal resection, appeared to be normal. In another study, McNeil *et al.*[11] showed normal fat stores in a small number of ileostomy patients, but these were assessed by a technique which is prone to considerable errors in such situations[12].

Finally it is important to stress that, despite having demonstrated normal body stores of water and salt in our patients after conventional ileostomy and also after the new operation of ileoanal J pouch, these patients depend on renal conservation mechanisms to compensate for their obligate faecal losses of salt and water. These compensatory mechanisms are known to increase the incidence of renal calculi in ileostomy patients and may also result in similar problems in patients after ileoanal anastomosis with J pouch[13].

Acknowledgements

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Surgical correction of the efferent ileal limb for disordered defaecation following restorative proctocolectomy with the S ileal reservoir

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The S ileal reservoir has been superseded in this unit but 76 patients had this operation between 1976 and 1983. Forty-one (54 per cent) patients had to catheterize the reservoir to evacuate faeces and this was primarily due to the long efferent ileal limb. In six patients, the need to catheterize and other problems with defaecation were such that surgical correction of the efferent ileal limb was undertaken. These six patients are reported. Presenting features were the need to catheterize the reservoir, difficulty in catheterizing, faecal incontinence, stenosis of the efferent ileal limb and transanal prolapse of the efferent ileal limb. All patients had an excessively long efferent ileal limb of 8 cm or more which was resected and reanastomosed to the anal canal. The resection was performed endoanally in three patients but was successful in only one. In the two patients in whom endoanal excision was unsuccessful and in the remaining three resection of at least 5 cm was performed transabdominally with endoanal reanastomosis. Three of these five patients were converted from catheterizing the reservoir to spontaneous evacuation, but two patients still needed to catheterize. All six patients benefited in terms of the need for, or frequency of, catheterization, or by improvement in continence. Excessive length of the efferent limb of an S ileal reservoir may cause unsatisfactory defaecation, which may be improved by partial resection. The transabdominal route is recommended for the resection, with endoanal reanastomosis. This surgery is potentially problematic and, although no anastomotic leakage was encountered, a covering loop ileostomy is recommended.

Keywords: Restorative proctocolectomy, ileal reservoir, ulcerative colitis, familial adenomatous polyposis

Restorative proctocolectomy with an ileal reservoir anastomosed to the anus is an operation that is still evolving. The S ileal reservoir was developed by Parks[1] and was initially used in this unit, but it was superseded because of problems with evacuation of faeces. In this type of reconstruction the reservoir is connected to the anus by a long conduit of ileum, termed the efferent ileal limb[1]. This is thought to be the reason why many patients with this particular type of reservoir never achieved spontaneous defaecation[2], and in current designs the reservoir is anastomosed directly to the anus without an intervening conduit[3]. Seventy-six patients had an S ileal reservoir at this hospital and 41 (54 per cent) of these needed to catheterize the reservoir in order to evacuate faeces[4].

In six patients, difficulty in catheterizing the reservoir and other problems with defaecation were so severe that surgical correction was required. These six patients and the principles of the corrective surgery are described.

Patients and methods

Six patients underwent restorative proctocolectomy with formation of an S ileal reservoir connected to the anus by an efferent limb of ileum which was anastomosed to the anal canal by an endoanal technique[1]. The indication for the operation was ulcerative colitis in four patients and familial adenomatous polyposis in two (*Table 1*). In all cases a long efferent limb connected the ileal reservoir to the anus. This was an intentional feature of the surgical technique practised in the unit at the time and was made approximately 5 cm in length. The specific problems with the efferent limb that resulted in the need for corrective surgery are shown in *Table 1*.

In all cases tests of anorectal physiology were performed before and/or after surgery to the efferent limb and showed that resting and voluntary squeeze pressures were satisfactory. Resting anal canal pressures ranged from 55 to 75 cmH$_2$O, and voluntary contraction pressures ranged from 70 to 240 cmH$_2$O. The minimum normal values for our laboratory are 40 cmH$_2$O for resting pressure and 40 cmH$_2$O for voluntary contraction, and the results indicate that the defaecation problems were not related to inadequate function of the anal sphincters.

Surgical technique

In all six patients the efferent limb of the reservoir was resected. In three patients the first operation was performed endoanally, but this was successful in only one (patient no. 1). In the two patients in whom it was unsuccessful and another three, a transabdominal operation was performed (*Table 2*).

The abdomen was opened through the previous laparotomy incision, adhesions were divided and the reservoir was dissected out. No major difficulty was encountered in mobilizing the reservoir and in no case was the lumen entered. The efferent limb was dissected free in the pelvis, and finding the plane between bowel and pelvic wall was frequently difficult.

No problem was encountered in making the reservoir reach the new anastomotic site, which was at the dentate line in all five patients. Mesenteric vessels did not have to be divided to gain extra length. The efferent limb was completely removed and the reservoir was then reanastomosed to the anal canal endoanally (*Figure 1*). Anastomoses were performed with interrupted 2/0 polyglactin 910 (Vicryl®, Ethicon Ltd., Edinburgh, UK) in one layer. All transabdominal excisions of

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Table 1 *Age, diagnosis and indications for surgery in six patients*

Patient no.	Age* (years)	Diagnosis	Indications	Follow-up† (months)
1	29	Ulcerative colitis	Faecal incontinence Straining Transanal efferent limb prolapse	53
2	48	Ulcerative colitis, Charcot–Marie–Tooth disease	Faecal incontinence Difficulty catheterizing Efferent limb stricture	7
3	20	Familial adenomatous polyposis	Faecal incontinence Catheterizing	12
4	24	Familial adenomatous polyposis	Catheterizing	21
5	25	Ulcerative colitis	Difficulty catheterizing Efferent limb stricture	12
6	48	Ulcerative colitis	Faecal incontinence Catheterizing	42

*At time of last corrective surgery; †from time of last corrective surgery

Table 2 *Year and nature of previous and corrective operations*

	Previous operations		Corrective operations	
Patient no.	Year	Operation	Year	Operation
1	1981 1983	S reservoir Marlex®* repair for efferent limb prolapse: unsuccessful	1984	Endoanal excision of efferent limb (5 cm); Marlex®* left in place
2	1977 1979	S reservoir Postanal repair for incontinence: unsuccessful	1988	Transabdominal excision of efferent limb (5 cm)
3	1982 1985	S reservoir Endoanal excision of 3 cm of efferent limb: unsuccessful	1987	Transabdominal excision of efferent limb (5 cm)
4	1981	S reservoir	1986	Transabdominal excision of efferent limb (9·5 cm)
5	1981	S reservoir	1987	Transabdominal excision of efferent limb (5 cm)
6	1980	S reservoir	1985	Endoanal excision of efferent limb: failed; transabdominal excision of efferent limb (8 cm)

*C.R. Bard Incorporated, Massachusetts, USA

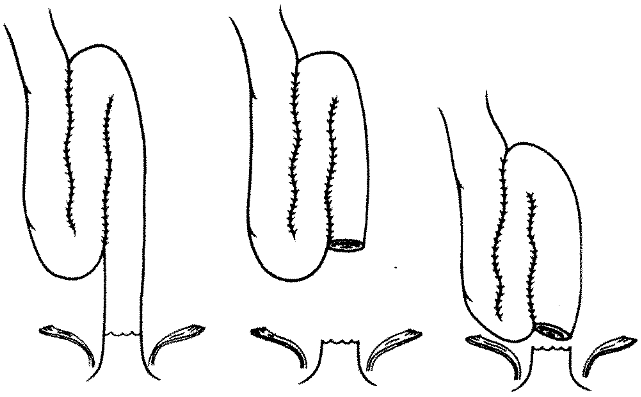

Figure 1 *Original design of the S ileoanal pouch showing the long efferent limb (left). This is excised (centre) and reanastomosed to the anal canal at the dentate line (right)*

the efferent limb were covered by a defunctioning asymmetric loop ileostomy. There was no mortality and the only morbidity was postoperative ileus lasting between 2 and 4 days.

The pouch–anal anastomosis was examined without anaesthesia in the outpatient department and subsequently under anaesthesia between 6 and 8 weeks after formation. All anastomoses were satisfactory and the ileostomies were closed during the same period of anaesthesia. No complications of ileostomy closure were encountered.

Results

The barium enema (pouchogram) of an S pouch with a long efferent limb (patient no. 2) is shown in *Figure 2*. *Figure 3* shows a similar study in the same patient after excision of the efferent limb.

The functional results after the final operation are shown in *Table 3*. Previous unsuccessful operations are shown in *Table 2*. In two patients a stenosis of the efferent limb was associated with the symptoms and this was removed as part of the resection. All patients were improved in terms of frequency of defaecation, conversion from catheterization to spontaneous evacuation, or relief from or improvement in faecal incontinence. Three of the five patients who needed to catheterize before surgery attained spontaneous evacuation afterwards.

Discussion

The S ileal reservoir was the first design to be used in the operation of restorative proctocolectomy in which an ileal reservoir is anastomosed to the anus[1]. The initial design deliberately included a long efferent ileal limb to minimize the risk of incontinence. With time, this was found to be unnecessary and it became apparent that the efferent limb was itself often responsible for dysfunction, especially difficulty in evacuation[1].

Table 3 *Function before and after excision of efferent ileal limb*

Patient no.	Bowel action before final operation	Bowel action after final operation
1	13 in 24 h (spontaneous); four per night Incontinent	3–4 in 24 h (spontaneous); 0 per night Continent
2	12 in 24 h (catheterizing) Nocturnal incontinence	6 in 24 h (spontaneous); 1 per night Slight incontinence Two pads in 24 h
3	7 in 24 h (catheterizing) Incontinent	8 in 24 h (spontaneous) Continent
4	3 in 24 h (catheterizing)	3 in 24 h (spontaneous)
5	6 in 24 h (catheterizing)	3–10 in 24 h (catheterizing) Some leakage
6	9 in 24 h (catheterizing) Incontinent	6 in 24 h (catheterizing) Continent

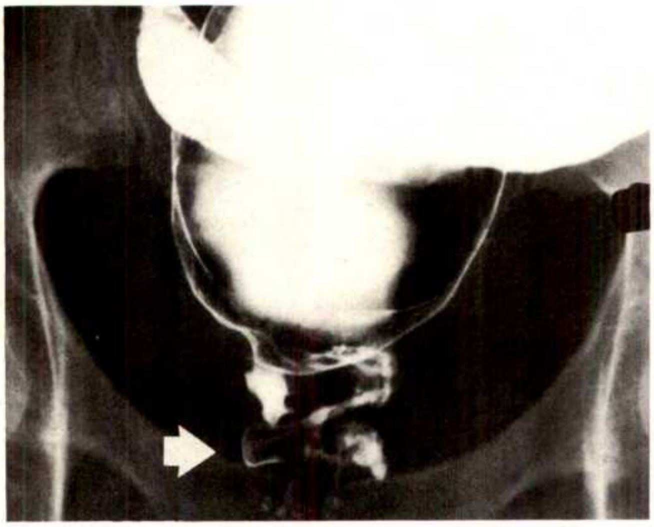

Figure 2 *Barium enema (anteroposterior view) showing long efferent ileal limb (arrowed). There is also a fistulous track just above the arrow*

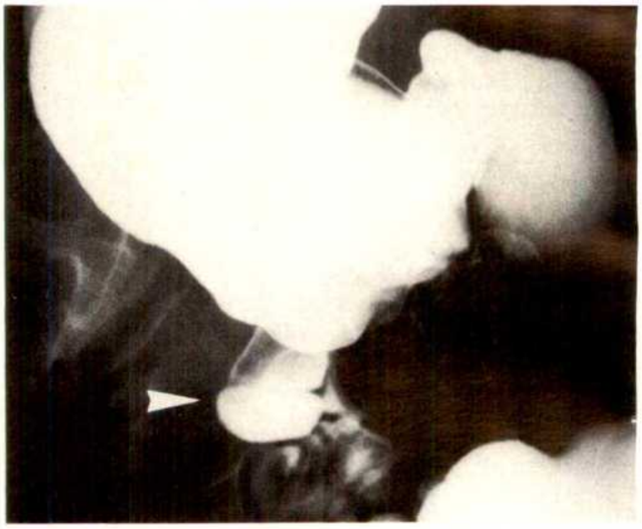

Figure 3 *Barium enema (anteroposterior view) after excision of the efferent limb of the ileal reservoir. The region of the ileoanal anastomosis is arrowed*

Fifty-four per cent of the patients with the original S reservoir needed to catheterize transanally to achieve evacuation[4]. While catheterization is appropriate for the Kock reservoir[5], it is not when there is an anal anastomosis with an intact sphincter mechanism. The efferent ileal limb merely makes spontaneous defaecation more difficult and the need for catheterization more likely. For this reason its length has been gradually reduced in units using this design of reservoir. A short limb of 2–3 cm or less leads to improved results with as few as 4 per cent of patients needing to catheterize[6,7].

The presence of the efferent ileal limb seemed to be the prime cause of the defaecation disorder in our patients, but other factors also exist. Stenosis occurred in two patients and this was thought to have an ischaemic origin in patient no. 5 from the histology of the excised segment. The stenosis that occurred in patient no. 2 was at the exit of the reservoir and was short (1 cm in length). Although the aetiology is uncertain it may be that repetitive catheterization caused traumatic ulceration with consequent fibrosis. Strictures sometimes occur at the ileoanal anastomosis but these are usually treated by dilatation rather than by excision.

When catheterization is obligatory and accompanied by faecal incontinence, or is hampered by efferent limb stenosis, surgical correction should be considered. This is especially so in this group of patients who have opted for a restorative procedure because of a desire to defaecate normally.

From the experience with these six patients two main conclusions can be drawn. First, excision of the entire efferent ileal limb should be the main aim of surgery, and such a procedure can be expected to improve symptoms. Second, transabdominal excision of the efferent ileal limb is likely to be more effective than an endoanal approach, although the latter may be tried in the first instance as it is a lesser procedure with the advantage that a covering temporary ileostomy is avoided. In those cases having transabdominal excision it has been our practice to cover the procedure with a defunctioning loop ileostomy. Although we have no evidence to show that it is necessary, we regard it as a prudent precaution against the consequences of anastomotic leakage.

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Case report

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Pneumatosis coli: a source of diagnostic confusion

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We report two sisters with pneumatosis coli who were destined for colonic resection for presumed familial adenomatous polyposis.

Case 1

A 57-year-old nursing sister presented to her general practitioner in 1988 with tenesmus and change of bowel habit. Surgical referral followed, with marked polyposis being found on sigmoidoscopy and colonoscopy. Four years earlier the patient had undergone a barium meal, sigmoidoscopy and barium enema for abdominal pain. These were normal. A family history of polyposis was not present. As a result of the 1988 findings proctocolectomy was planned. The patient was referred to St. Mark's Hospital for assessment of her suitability for pouch reconstruction. Outpatient rectal polyp biopsy revealed inflammatory changes only. The patient was referred for colonoscopy which revealed multiple 'polyps' distributed throughout the colon. Because of their tense and shiny appearance, they were thought to be cysts rather than polyps. Needle puncture was performed on several of the cysts (*Figure 1*) which resulted in immediate deflation and disappearance (*Figure 2*). Representative cyst biopsies were normal. Use of the biopsy forceps did not result in cyst deflation. No further treatment is planned.

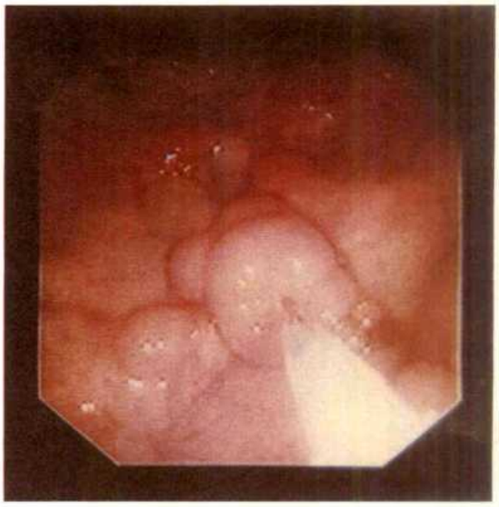

Figure 1 *Before cyst deflation*

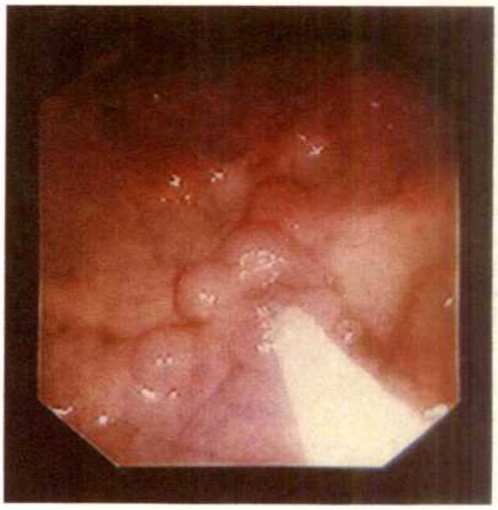

Figure 2 *After cyst deflation*

Case 2

The 65-year-old sister of the previous case presented as part of family assessment in view of the presumed polyposis of her sister. Symptoms consisted of colicky lower abdominal pain and occasional passage of mucus per rectum. Abdominal, rectal and sigmoidoscopic examinations were normal. Barium enema was suggestive of polyposis. Colonoscopy was performed; puncture of some of the 'polyps' resulted in their deflation and biopsy was normal.

Discussion

Colectomy and ileorectal anastomosis for pneumatosis simulating polyposis has previously been reported[1,2], as has a familial association[3]. Colonoscopy and biopsy confirmation of the diagnosis are necessary in view of the difficulty in differential diagnosis when based on barium enema alone[4]. If gross appearances are suggestive of cysts rather than polyps, needle deflation should be attempted. It is not enough to rely on biopsy deflation as too superficial a bite may be taken. In this way misdiagnosis and its consequences may be avoided.

Acknowledgements

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Role of intraoperative prograde colonic lavage and a decompressive loop ileostomy in the management of transmural amoebic colitis

A prospective analysis is presented of a selected group of 45 consecutive patients with transmural amoebic colitis treated by laparotomy, colonic lavage and ileostomy (phase 1 surgery) over 3 years. The diagnosis of amoebic colitis and amoebic perforation of the bowel were difficult and therefore all patients with 'acute abdomen' had proctosigmoidoscopy and a trial of metronidazole for 24–48 h before laparotomy. At laparotomy, adhesive wraps were present in all patients; 13 perforations were exposed by inadvertent disturbance of adhesive wraps but were successfully closed by suture to any available organ in close proximity, such as the omentum or small bowel. Four patients (9 per cent) died after phase 1 surgery. After 6 weeks when the acute disease had healed, 33 of the remaining 41 patients (80 per cent) required closure of ileostomy only, five had resection of stricture and three (7 per cent) needed stricturoplasty (phase 2 surgery). Two patients (5 per cent) died after phase 2 surgery. Thus, in surgery for transmural amoebic colitis adhesive wraps should not be disturbed as they mechanically protect the peritoneal cavity from faecal soiling when perforation occurs. The colon should be emptied by lavage and the faecal stream diverted to avoid secondary bacterial effects.

Keywords: Transmural amoebic colitis, on-table prograde lavage, colonic lavage, ileostomy decompression

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At laparotomy performed for transmural amoebic colitis, the most striking findings are adhesive wraps burying ischaemic foci of the colon and a clean peritoneal cavity[1]. Adhesive wraps are defined as omental and peritoneal adhesions attracted by ischaemic intestine. Intraoperative assessment of the extent and degree of the buried ischaemic process in transmural amoebic disease involves dismantling the wraps. This may expose perforations and result in faecal soiling of the peritoneum with its attendant sepsis. Resectional surgery, which requires the wraps to be undone, is associated with considerable mortality rates ranging from 43 per cent[2] to 55 per cent[3]. Our own resectional surgery experience reported in 1982[4] revealed a mortality rate of 24 per cent (12/50) and our published non-resectional surgery mortality rate is 12 per cent[5].

A laparotomy finding of a clean peritoneal cavity in the presence of advanced transmural amoebic colitis[1] suggested that the result of surgery might be improved if adhesive wraps were not disturbed and the bacterial contamination by intestinal organisms from the lumen of the colon were removed by perileotomy on-table antegrade colonic lavage with removal of the colon contents through the anus[6]. The lavaged colon might be defunctioned by an ileostomy maintained for 6 weeks before closure. This paper presents a prospective analysis of a selected group of 45 consecutive patients with transmural colitis treated by laparotomy, colonic lavage and ileostomy.

Patients and methods

During the period 1 June 1984 to 1 June 1987, 105 patients with suspected amoebic colitis with complications were admitted and managed by one of six surgical units at King Edward VIII Hospital, Durban, South Africa. All these patients were peri-urban Africans whose nutritional status was poor on admission but improved dramatically as they recovered from illness. This is inevitably a selected group of patients with as many patients having been diagnosed and treated conservatively in medical wards by physicians or in consultation with other surgeons. Of the 105 patients, 60 improved on conservative treatment with metronidazole plus fluid and electrolyte replacement and became clinically better in 24–48 h. Forty-five patients (43 per cent) were judged to require surgical intervention; only these will be discussed further in this report. Their presumed diagnoses at referral are listed in *Table 1*. There were 35 men (78 per cent) and 10 women (22 per cent); the mean age was 44 years (range 20–71 years). The main clinical features are shown in *Table 2*.

Diagnosis of amoebic colitis

The proof of diagnosis was by (1) amoebic ulceration found at sigmoidoscopy; (2) identification of haematophagous amoebae in stools or tissue biopsies; and (3) finding of characteristic adhesive wraps at operation (*Table 2*). All patients with abdominal pain, diarrhoea, proctitis or an 'acute abdomen' who were suspected of having amoebic colitis had proctosigmoidoscopy, tissue and slough biopsies and fresh stool examination for haematophagous amoebic trophozoites.

Plain radiographs of the abdomen were taken to exclude the presence of gas under the diaphragm or tissue mottling indicating extraluminal gas which constitute indications for urgent surgical intervention. All patients were then given a trial of metronidazole 800 mg orally 8-hourly if possible, or 500 mg intravenously 8-hourly for 24–48 h. Patients with radiological evidence of perforation, with peritonitis, or those who failed to improve or deteriorated on conservative management as indicated by continuing distension, toxicity or persistent catastrophic diarrhoea, were subjected to laparotomy. Amoebic gel diffusion testing (precipitin test) played a very small part in the immediate diagnosis of transmural disease. The test takes several days to perform and since Durban is an endemic area a positive result only signifies past or present infection and a negative result can be found in the presence of severe colitis.

Operative strategy and technique

The operative principles in transmural amoebic colitis are: (1) establishing the diagnosis; (2) minimal disturbance of adhesive wraps;

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Table 1 *Referral diagnoses in 45 consecutive patients with transmural amoebic colitis requiring surgical intervention*

	No. of patients
Complicated amoebiasis	14 (31)
Perforated amoebic colitis	11
Amoebic colitis + ruptured amoebic liver abscess	3
Acute abdomen	27 (60)
Intestinal obstruction	5
Herbal intoxication	8
Peritonitis	8
Perforated typhoid	2
Severe gastroenteritis	3
Perforated appendix	1
Others	4 (9)

Values in parentheses are percentages

Table 2 *Main clinical features in 45 consecutive admissions with complicated amoebic colitis requiring surgical intervention*

	No. of patients
Length of history	
0–1 week	32 (71)
>1 week	13 (29)
Symptoms	
Diarrhoea	39 (87)
Abdominal pain	37 (82)
Blood in stool	16 (36)
Signs	
Abdominal tenderness	44 (98)
Localized	16 (36)
Generalized	28 (62)
Abdominal distension	30 (67)
Masses	13 (29)
Proof of diagnosis	
Ulceration at sigmoidoscopy	35 (78)
Haematophagous amoebae in stool or biopsy	21 (47)
Operative findings of some adhesive wraps	45 (100)
Amoebic gel diffusion positive	41 (91)

Values in parentheses are percentages

(3) avoidance of resectional surgery; (4) prograde colonic lavage; and (5) defunctioning ileostomy.

At operation all patients were placed in the Lloyd-Davies position with facilities for carrying out on-table prograde colonic lavage as previously described with discharge of effluent through an anal tube[6]. Through a short lower midline incision, with minimal disturbance of the adhesive wraps, the terminal ileum was isolated and brought out as a loop. An ileostomy prograde colonic lavage was performed[6]. When it was difficult to identify the terminal ileum, any distal small bowel presenting at the incision was used and the prograde direction of irrigation established by a trial of clamping one limb of the ileotomy while irrigating through the other. Colonic distension by irrigation fluid is common, can be frightening and indicates that in amoebic transmural disease of the large bowel there is usually an element of obstruction which may present clinically as so called 'toxic megacolon'[7]. Compression with warm packs over the incision minimizes the distension of the colon. Abdominal agitation is necessary to speed up the lavage procedure.

If leakage of the irrigating fluid, usually due to inadvertent disturbance of caecal or sigmoid wraps at initial ileal mobilization, was detected, the perforation was closed by simple suturing with an absorbable material or by patching with omentum.

After colon irrigation the ileotomy was converted into a loop ileostomy whose proximal and distal limbs were intubated to allow postoperative egress of fluid and gas. This prevents the build-up of intracolonic pressure which can disrupt the protective wraps.

The liver was palpated in an endeavour to exclude an abscess. Large abscesses were intubated blindly percutaneously and the drain led into a sterile closed system. The abdominal cavity was then closed in mass fashion with nylon. If there was no gross contamination the skin was also closed. Finally, the rectal tube was removed and post-laparotomy anal dilatation performed to help produce incontinence, ensuring postoperative egress of fluid and gas.

Before ileostomy closure, usually after 6 weeks, the colon was assessed by barium enema for strictures as these may require resection and anastomosis or stricturoplasty depending on the calibre of the lumen (*Figure 1*).

Results

Most of our patients with transmural amoebic colitis requiring surgical intervention presented with diarrhoea (87 per cent), abdominal pain (82 per cent), abdominal tenderness (98 per cent), and rectal ulceration (78 per cent). Haematophagous amoebae were isolated in about half the patients (*Table 2*).

Preoperative misdiagnosis

Amoebiasis was missed preoperatively by the referral source in 69 per cent of patients (*Table 1*) and by the operating surgeon in 18 per cent (eight patients). Five of these patients were operated upon for a perforated viscus, two for intestinal obstruction and one for rectal bleeding. Four patients with haematophagous trophozoites of *Entamoeba histolytica* in stools and rectal ulcers on sigmoidoscopy had a negative gel diffusion test (*Table 2*).

Operative procedures

Table 3 summarizes the phase 1 operative procedures performed in 45 patients. All had a successful colonic lavage and ileostomy decompression. During isolation of the terminal ileum, 13 perforations were exposed which required watertight closure to allow effective colonic lavage. Six patients had a blind drainage of an amoebic liver abscess.

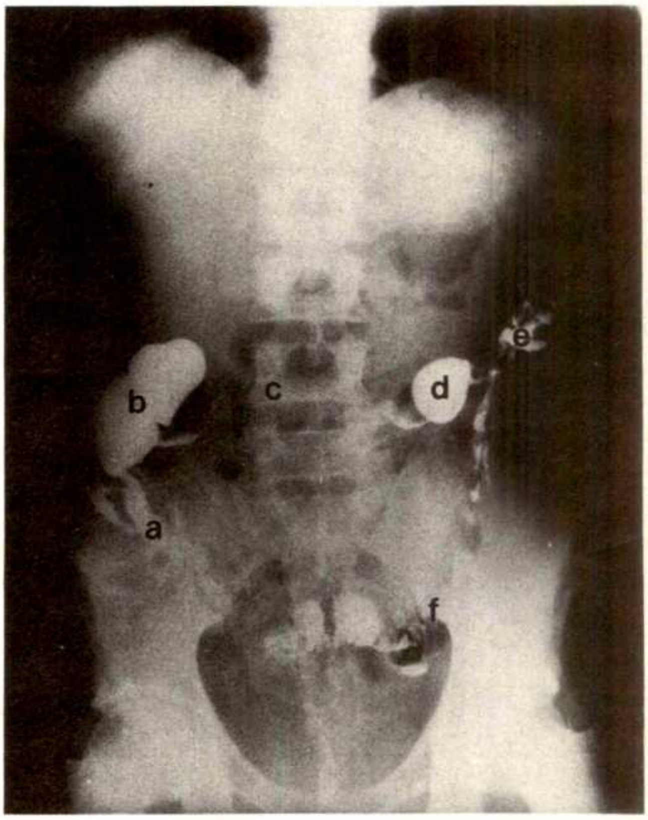

Figure 1 *Barium enema of a patient with amoebic colitis 6 weeks after on-table prograde lavage and decompressive ileostomy (a). The ascending colon (b) has been spared while the proximal transverse colon (c) has been completely destroyed. Distal transverse colon (d) has been spared. A long ischaemic stricture extends from the splenic flexure (e) to sigmoid colon (f). Bowel continuity was established by ascending colon-sigmoid colostomy, resecting the intervening strictured colon*

Table 3 *Operative procedures in 45 consecutive patients with complicated amoebic colitis (phase 1 operation)*

Operative procedures	No. of cases
Colonic lavage + ileostomy decompression	45
Closure of perforation exposed during laparotomy	
Caecum	10
Sigmoid	3
Drainage of associated large amoebic liver abscess	6

Complications

Most postoperative complications occurred during the early part of this study. Compression of the ileostomy by the abdominal wound (strangulation) or tight ileostomy limbs were the main causes of small bowel fistulae in five patients. Partial wound dehiscence occurred in three patients but did not require repair. One patient was readmitted with a colovesical fistula after colorectal anastomosis and another developed a colosplenic artery fistula 3 weeks after an uneventful colon lavage and ileostomy decompression. Both these patients died.

Mortality

Six patients in this series died, giving an overall mortality of 13 per cent. Four patients (9 per cent) died after colonic lavage and ileostomy decompression (phase 1 surgery). Of these one died from amoebic colitis and pulmonary oedema, and two died of metabolic derangements at 6 weeks and 3 months when they refused to eat following total parenteral nutrition. Post mortem examination of both patients revealed a completely healed colitis. The patient who remained with an ileostomy for 3 months was grossly malnourished, on hyperalimentation and was considered unfit for surgery. The fourth patient collapsed and died after being ambulant 1 week after surgery; autopsy examination was not obtained. Two patients (5 per cent) died after closure of ileostomy (phase 2 surgery) from colovesical and coloarterial fistulae.

Establishment of bowel continuity

Table 4 indicates the operative procedures performed to establish bowel continuity when the disease had healed. Most patients (80 per cent) required simple ileostomy closure only. Others had strictures which required segmental resection (five patients) or stricturoplasty (three patients) to establish bowel continuity (*Figure 1*). The main indication for stricturoplasty was a very short stricture with long segments of normal colon proximally and distally. Bowel was opened longitudinally and closed transversely. Multiple stricturoplasty with or without resection could be performed.

Discussion

The management of complicated transmural amoebic colitis is controversial and its mortality is high whether patients are managed conservatively[8] or surgically[9]. In 1962 Wilmot[10] advocated conservative management of transmural amoebic colitis, accepting a mortality rate of 42 per cent because 'surgery can only make the situation worse'. Seventeen years later Vajrabukka *et al.*[3] advised resection with exteriorization of the ends associated with a mortality rate of 55 per cent as 'the best operative treatment ...'. Eggleston *et al.*[2], in 1978, preferred diversional surgery with a mortality rate of 43 per cent; all of their patients with an associated amoebic liver abscess died. They believed that 'faecal diversion with a wide drainage is the treatment of choice for amoebic perforation of the colon'. In 1987, holding the same views, Eggleston's mortality rate stood at 50 per cent[11].

These variations in the management of transmural amoebic colitis are a direct result of the currently held view that the diseased colon is as friable as damp blotting paper and as difficult to handle[12]. These views ignore important clinicopathological observations in complicated amoebic colitis. Those who advocate conservative management or faecal diversion only probably disregard the role of bacterial contamination. Those who regard resectional surgery as the treatment of choice probably neglect the importance of the adhesive wraps in containing the faeces within the colonic lumen as well as effects of the inevitable bacterial contamination of the peritoneal cavity during the resection in causing fatal sepsis in these desperately ill patients. Evidence collected from our previous studies of transmural amoebic colitis has shown an important pathological process which consists of thrombosis of colonic arterial vessels with subsequent ischaemic necrosis of varying degrees[13].

Adhesive wraps help in walling off potential free perforations subsequent to ischaemia and have a capacity to revascularize the ischaemic colon[1]. Disturbing these adhesive wraps has a deleterious effect[14]. Because our previously recommended segmental resection of ischaemic colon[4] was still attended by significant morbidity and mortality rates, we have reasoned that, in the presence of efficient adhesive wraps around transmural colitis, 'decontaminating' the colon by lavage and defunctioning ileostomy might improve prognosis. The results reported in this study support our hypothesis and show an encouraging improvement in outcome over medical management[10], radical resection[3] and our segmental resection[4]. An important additional factor in prognosis has been early identification of patients with transmural disease, their assessment and appropriate active sequential management. Transmural amoebic colitis may mimic many surgical conditions (*Table 1*) and unless it is considered in a differential diagnosis it is likely to be missed, especially in areas where it is not endemic. The great variation in the clinical presentation (*Table 2*) enhances the chances of misdiagnosis. Anticipation of surgical misdiagnosis is very important as haematophagous amoebae were identified in only half the patients (*Table 2*). Adhesive wraps are a better guide to diagnosis and were present in all our patients at laparotomy.

Sequential management in patients with diagnosed amoebic colitis involves treatment with metronidazole for 24–48 h. If amoebiasis is suspected failure to identify haematophagous amoebae should not delay treatment with metronidazole because the mortality of complicated amoebic colitis is so high[3]. If no clinical improvement occurs, phase 1 surgery is carried out since metronidazole cannot deal with established ischaemic necrosis of transmural amoebic colitis.

Colonic lavage and ileostomy decompression were technically successful in all our 45 patients (*Table 3*). Important points need to be identified in the operative procedure. The lower midline incision is used to lessen reduced ventilatory effort, but caution is needed in the separation of adhesions of sigmoid colon or loops of small bowel from the anterior abdominal wall. Isolating the terminal ileum involves some dismantling of the adhesive

Table 4 *Operative procedures performed to establish bowel continuity after ileostomy decompression in 41 patients with complicated amoebic colitis (phase 2 surgery)*

Operative procedure	No. of patients
Closure of ileostomy only	33* (80)
Resection of stricture	
Colorectal anastomosis	4 (12)
Coloanal anastomosis	1
Stricturoplasty	3 (7)
Total	41 (100)

Values in parentheses are percentages. * Fifteen patients had a normal barium enema, seven had clinically insignificant radiological strictures, ten had perforations closed at phase 1 surgery and one patient had free air under the diaphragm at the initial admission wraps around the contiguous loops of large and small bowel. Thirteen perforations (in 13 patients) occurred or were exposed during mobilization of the terminal ileum (*Table 3*). All were successfully closed and made watertight by patching with omentum or small bowel or by simple closure with single layer absorbable sutures. No effort was made to avoid the narrowing of the colon lumen during closure of the perforation. We have already noted that Eggleston *et al.*[2] reported that all their patients with amoebic liver abscess who required surgery for colitis died. In our present series six patients had an associated large abscess which was drained by percutaneous intubation and they all survived.

Although complications have occurred in this series, they were less severe than those previously reported on conventional resectional treatment of transmural disease and most occurred during the earlier part of this study. Twisting and obstruction (even gangrene) of the ileostomy was the most common cause of small bowel fistulae after operation in these patients. All ileostomies are now intubated with a tube drain to prevent rotation which may occur. Wound infection is minimized by closing primarily only if there has been no overt soiling. Stricturing of the colon is the main and inevitable consequence of the vascular effect of transmural disease when the gut is left *in situ* (*Figure 1*), but this can be dealt with electively. The patients are fit and well prepared so that the results are good. Leaving ischaemic and necrotic bowel within the peritoneal cavity did not adversely affect the outcome and this is attributed to the mechanical barrier effect and neovascularization by the adhesive wraps. Adhesive wraps, so characteristic of transmural disease, should not be disturbed as they mechanically protect the peritoneal cavity from faecal soiling when perforation occurs[1].

To evaluate the beneficial effect of adhesive wraps in other clinical settings, a study is underway in which the adhesive wraps are surgically created by suturing omentum to bowel to prevent re-perforation in typhoid disease or breakdown in anastomoses of irradiated bowel; initial results are encouraging.

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Endoscopic sphincterotomy for the palliation of ampullary carcinoma

Palliative endoscopic sphincterotomy was performed on 17 patients with adenocarcinoma of the ampulla of Vater. An endoprosthesis was inserted immediately after the sphincterotomy in four of the patients. Fourteen patients made uncomplicated recoveries from the procedure and their jaundice resolved completely. Early complications developed in three patients. One patient died from haemorrhage. Two patients, both of whom had an endoprosthesis, developed cholangitis. The endoprosthesis was removed and another inserted in one patient and the other underwent surgery. Both thereafter made uncomplicated recoveries. Jaundice subsequently recurred in eight patients and further endoscopic treatment was successful in five of these patients. Eleven patients died between 4 days and 23 months after the sphincterotomy with a median survival of 12 months. Four patients remain alive between 3 and 17 months after treatment. The results indicate that reasonable palliation can be achieved safely by endoscopic sphincterotomy.

Keywords: Vater's ampulla, carcinoma, sphincterotomy, endoscopy, cholangiopancreatography, retrograde

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Carcinoma of the ampulla of Vater is one of the few causes of malignant biliary obstruction for which a resection can offer a reasonable prospect of long survival. The 5-year survival rate following pancreaticoduodenectomy is 20–50 per cent[1–6] and similar results can be achieved by the local resection of small tumours[4,5]. Resection of an ampullary tumour is, however, a major procedure with a high incidence of mortality and morbidity, and palliative treatment is more appropriate for many elderly patients. Palliation is usually achieved by a surgical bypass, but the results are generally poor in terms of morbidity, mortality and prognosis. Malignant biliary obstruction can be relieved satisfactorily by the endoscopic insertion of an endoprosthesis, but this technique has been almost entirely restricted to the palliation of pancreatic and bile duct cancer[7,8]. The satisfactory palliation of ampullary cancer by endoscopic sphincterotomy has been reported briefly[6,7], but the safety and effectiveness of the technique are uncertain. We report here on our experience of endoscopic sphincterotomy in 17 patients with ampullary cancer.

Patients and methods

Between June 1983 and May 1988, 17 patients with adenocarcinoma of the ampulla of Vater underwent a palliative endoscopic sphincterotomy. There were 11 women and six men with a median age of 76 years (range from 65 to 86 years) All patients had presented with deep jaundice and had been referred for endoscopic retrograde cholangiopancreatography after an ultrasound examination had demonstrated biliary dilatation Surgical or percutaneous biliary decompression had not been attempted. The patients were considered to be unfit for a resection of the tumour because of cardiovascular disease (five patients), respiratory disease (three patients), recent stroke (one patient), alcoholism (one patient), hepatic metastases (one patient), dementia (one patient) or general frailty (five patients).

Coagulation deficiencies were corrected and an intravenous antibiotic (piperacillin 1 g or cefuroxime 750 mg) was administered 1 h before the procedure Duodenoscopy and retrograde cholangiography were carried out under intravenous sedation using an Olympus JF-1T (Olympus-Keymed, Southend, UK) or a Pentax FD-34A® (Pentax UK Ltd., Harrow, UK) duodenoscope. All patients had a typical ampullary tumour and gross dilatation of the bile ducts. The diameters of the common bile ducts (as measured from the cholangiogram using the duodenoscope as a reference) ranged from 1·4 to 3 1 cm with a median of 2 5 cm The sphincterotomies, or more correctly tumourotomies, were performed using a Classen-Demling sphincterotome and blended diathermy. In all cases the tumour was incised to allow exposure of normal bile duct mucosa. We inserted an endoprosthesis immediately after the sphincterotomy in four patients because no definite mechanical obstruction was found and we feared that sphincterotomy alone might not provide adequate decompression. Although these patients all had a bile duct which was markedly dilated right down to the ampulla, the ampulla itself was not particularly stenotic and a cannula could be passed with ease. A single 15 cm 10 French gauge Leung-Cotton type endoprosthesis was inserted across the tumour in all four patients Radiological screening confirmed that the endoprostheses were in satisfactory positions (that is, the upper end in the proximal common bile duct and the lower end protruding into the duodenum) and bile was seen to drain freely After the procedure the patients received at least one further dose of antibiotic, and were allowed to eat and drink when they had recovered from the sedation.

A histological diagnosis of adenocarcinoma was obtained in 15 patients Biopsies were taken either before or immediately after the sphincterotomy in all patients and were positive in ten patients A histological diagnosis was obtained from biopsies taken at later endoscopies in a further four patients and from tissue obtained at a later laparotomy in one further patient. An unequivocal cytological diagnosis of adenocarcinoma was obtained from brushings taken before the sphincterotomy in seven out of nine patients, and in two patients this was the only proof of malignancy.

Results

The results are summarized in *Table 1*. One patient died at home from a massive gastrointestinal haemorrhage 4 days after a sphincterotomy and the bleeding was assumed to have arisen from the sphincterotomy. Two of the four patients who had endoprostheses inserted developed cholangitis immediately after the procedure. The jaundice and cholangitis of one patient resolved completely after the endoprosthesis had been replaced. The endoprosthesis of the second patient was also replaced but this failed to produce any improvement. He was eventually treated successfully by a surgical bypass and removal of the endoprosthesis and survived for a further 13 months. The remaining 14 patients made uncomplicated recoveries from the procedure and the jaundice resolved completely in all cases The jaundice of the 15 patients who were successfully treated endoscopically took from 2 to 7 weeks (median 3 weeks) to resolve. The median stay in hospital after sphincterotomy was 3 days. The patient who required a laparotomy was discharged

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Table 1 *Results of endoscopic sphincterotomy*

Patient	Age (years)	Positive histology	Endoprosthesis	Early complication	Late complication	Survival time (months)
1	81	Yes	No	Haemorrhage	—	4 days
2	65	Yes	Yes	Cholangitis*	—	13
3	72	Yes	No	—	Jaundice*	12
4	81	Yes	No	—	Jaundice*	13
5	73	Yes	Yes	—	Jaundice and cholangitis*	7
6	77	Yes	No	—	Jaundice†	23
7	66	Yes	Yes	—	Jaundice and cholangitis†	5
8	85	Yes	No	—	Jaundice*	13
9	72	Yes	No	—	Jaundice†	15
10	80	Yes	No	—	Jaundice†	12
11	86	No‡	No	—	—	4
12	72	Yes	No	—	—	4
13	75	Yes	No	—	—	2
14	68	Yes	Yes	Cholangitis†	—	17, alive
15	79	No‡	No	—	—	7, alive
16	78	Yes	No	—	—	4, alive
17	82	Yes	No	—	—	3, alive

* Successfully treated by surgery; † successfully treated by endoscopy, ‡ positive cytology was obtained from these patients

22 days after the sphincterotomy. The remaining 16 patients were discharged between 1 and 15 days after the sphincterotomy and only two patients stayed for more than 6 days.

Eight patients developed recurrent jaundice between 4 and 11 months after the sphincterotomy. The jaundice was associated with cholangitis in two patients with endoprostheses. Further endoscopic treatment (that is, a further sphincterotomy, or the insertion or replacement of an endoprosthesis) was successful in five patients. The longest survivor experienced three episodes of recurrent jaundice and endoscopic treatment was successful on each occasion. Endoscopic treatment was unsuccessful in three patients because the tumour had grown to such an extent that cannulation was not possible. These patients underwent a biliary bypass and all survived the operation Seven patients remained free from jaundice; two died and four are alive at 3, 4, 7 and 17 months. No patient developed duodenal obstruction. The 13 patients who had died following a palliative sphincterotomy had a median survival of 12 months (mean of 9·5 months), and seven patients (54 per cent) lived for at least 1 year.

Discussion

The results of biliary–enteric bypass for the palliation of ampullary cancer are appalling. In the six most recent reports the operative mortality rate ranged from 17 to 60 per cent, with a collective rate of 32 per cent[2,4–6,9,10]. Furthermore, only approximately half the patients who survived the operation lived for more than 1 year, and in only one report did the overall 1-year survival rate exceed 50 per cent. In view of these poor results it is not surprising that attempts have been made to palliate the disease by endoscopic sphincterotomy. Leung *et al.* reported the relief of jaundice in eight out of nine patients[7], and Neoptolemos *et al.* achieved success in nine out of 13 patients[6]. In both reports the procedure appeared to have provided reasonable palliation and no mention was made of any late complications.

Our results confirm that endoscopic sphincterotomy is a highly effective and reasonably safe means of relieving the jaundice of ampullary cancer. There was only one procedure-related death and failure occurred in only one other patient. For the majority of patients the procedure was entirely free of complications and required only a brief stay in hospital The mortality and morbidity rates of the procedure were considerably lower than those reported after surgical bypass, and it is inconceivable that our patients could have been discharged so rapidly had a laparotomy been performed The results are particularly gratifying as at least three patients were considered to be unfit for a surgical bypass. The survival of patients following endoscopic sphincterotomy compares favourably with that of surgical bypass. The life expectancy after a successful sphincterotomy or bypass is similar but, as the mortality rate associated with sphincterotomy is lower, the overall survival rate of our patients was better than any of the reported results of surgical bypass.

We inserted an endoprosthesis immediately after the sphincterotomy in four patients because although there was gross biliary dilatation there did not appear to be any definite mechanical obstruction at the ampulla. We cannot explain this curious phenomenon but the obstruction may have been due to a flap-valve mechanism or a tumour induced disturbance of the biliary sphincter. The insertion of an endoprosthesis was, however, probably a mistake as all four patients developed cholangitis and it is possible that a sphincterotomy alone would have provided adequate drainage. We now suggest that endoprostheses should be reserved for patients in whom a sphincterotomy has been shown to be ineffective.

Our results illustrate the difficulty of obtaining a histological diagnosis from endoscopic biopsies Although an unequivocal histological diagnosis was eventually obtained in 15 of the 17 patients, biopsies taken at the time of the sphincterotomy were positive in only ten patients We found cytology to be helpful, but in three patients the initial diagnosis was based solely on the macroscopic appearance of the ampulla. Similar diagnostic difficulties have been reported by others[6]. In an attempt to improve the diagnostic yield we now take multiple biopsies and brushings both before and after the sphincterotomy.

The principal disadvantage of endoscopic palliation is the high incidence of recurrent jaundice. However, in our experience, the jaundice could be relieved endoscopically in over half the patients and the three patients who required a surgical bypass all survived the operation. Endoscopic treatment failed on three occasions because growth of the tumour prevented cannulation. Cannulation difficulties can be overcome by a combined percutaneous and endoscopic approach in which a guide-wire is first inserted transhepatically down the bile duct and through the sphincter of Oddi[11]. Although we have no experience of this technique for ampullary tumours its use is likely to reduce the need for surgical intervention. Endoscopic sphincterotomy will not, of course, prevent the development of duodenal obstruction but this complication has not so far occurred in our patients. Recurrent jaundice and duodenal obstruction are not peculiar to endoscopic palliation, and in one report of surgical bypass 23 per cent of patients required a second laparotomy[9].

Our results, and those of others, show that endoscopic sphincterotomy can provide reasonable palliation for patients with carcinoma of the ampulla of Vater and appears to be considerably safer than surgical bypass. The procedure has the advantages of requiring only a short stay in hospital and of being applicable to virtually all patients regardless of age or fitness We recommend greater use of the technique.

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Evaluation of the prognostic value of triple node biopsy in early breast cancer

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The prognostic information obtained by triple node biopsy (low axillary, apical axillary and internal mammary nodes) in 693 patients with early breast cancer has been reviewed. Results show that tumour site within the breast influenced which nodal groups were involved. The low axillary node contributed the most useful prognostic information. The involved apical node carried the worst prognosis. Either the internal mammary node or a low axillary node when positive alone carried the same prognostic weight. When both nodes were positive the prognosis declined to the level associated with apical node positivity. A double node biopsy of the low axillary node and either the apical or the internal mammary node gave the same maximum prognostic information as a triple node biopsy. The triple node biopsy technique can be used to divide patients into groups with vastly different prognoses.

Keywords: Node biopsy, lymph node, prognosis, breast cancer

Lymph node staging remains one of the most powerful predictors of prognosis in early breast cancer[1,2], but the optimal method by which to obtain this information is controversial[3–5].

The policy of the breast unit in Nottingham is a triple node biopsy, sampling nodes from the lower axilla, the apex of the axilla and the internal mammary chain[6]. Patients are stratified into three stages depending on which nodes are involved. This stage, along with the size and differentiation (grade) of the primary tumour, is used to calculate a prognostic index:

$$\text{Prognostic index} = \text{tumour size} \times 0{\cdot}2 + \text{grade } (1\text{–}3) + \text{lymph node stage A, B or C (scored 1, 2 or 3)}$$

This index can be used to divide patients with early breast cancer into three different prognostic groups and its accuracy has been confirmed by a prospective study[7]. It identifies a group of approximately 25 per cent of cases (index < 3·4) with an excellent prognosis – near to that of women who do not have breast cancer It identifies another group of approximately 25 per cent of cases (index > 5·4) with a very poor prognosis (50 per cent dead at 24 months) and between these a group with an intermediate prognosis (32 per cent survival at 5 years).

This study was undertaken to evaluate the prognostic information obtained by triple node biopsy (the specific contribution each node made to the lymph node stages), whether a double node biopsy would give similar information to a triple node biopsy, the influence of missing a node during sampling and the need to redefine the lymph node staging system

Patients and methods

The study included patients who presented with early operable invasive breast cancer Between October 1973 and February 1988, 1288 patients underwent a triple node biopsy

Strict inclusion criteria were used for this study Patients were required to be 70 years of age or less. Tumour size had to have been recorded in three dimensions. Tumours were bisected in the fresh state in two planes at right angles to one another and three dimensions were measured. Tumour size was taken as the maximum of these three measurements Tumour site within the breast had to be accurately documented Patients with Paget's disease or ductal carcinoma *in situ* were not included Of the 1288 patients who underwent triple node biopsy 693 fulfilled these criteria and form the basis of this investigation All patients were treated under the care of one surgeon (R W.B)

Sampling technique

After completion of the primary operation, one node was sampled from the lower axilla below the lateral border of the pectoralis minor muscle A second node was sampled from the apex of the axilla, adjacent to the axillary vein, by splitting the muscle fibres between the sternal and clavicular heads of the pectoralis major muscle. The third node was sampled from the internal mammary chain via the second interspace

Staging method

If all three nodes were negative for metastatic disease the stage was A, if only the low axillary node was positive the stage was B, and if either or both the apical or internal mammary nodes were positive the stage was C. The absence of lymphoid tissue on histological examination was considered negative for that specific biopsy site.

This staging system was based on work undertaken by Berg[8] who showed that the higher the level of lymph node involvement in the axilla the poorer the prognosis, and by Handley *et al.*[9,10] who showed that involvement of the internal mammary node carried a poorer prognosis compared with involvement of the axilla alone.

The site of the tumour within the breast was based on clinical examination and referenced to an imaginary vertical line through the nipple Tumours lying behind the nipple/areola complex were considered central

Treatment and follow-up

The majority of patients (97·2 per cent) underwent simple mastectomy A small number (2·8 per cent) were treated by tumorectomy and whole breast irradiation or a subcutaneous mastectomy No patient received adjuvant systemic therapy after primary treatment. Patients were reviewed at 3-monthly intervals for the first 24 months, 6-monthly up to 5 years and thereafter annually

Locoregional recurrence was treated by local surgery, local radiotherapy or both, depending on the nature of the recurrence. Distant metastatic disease was treated by endocrine therapy and by systemic chemotherapy on disease progression

Prognostic measurements and statistics

The prognostic information from the different subgroups based upon lymph node status was compared by survival curves constructed using the life table analysis method[11] The χ^2 method as described by Mantel[12] was used to determine statistical differences between two curves. The method of Armitage[13] was used to determine statistical differences between more than two curves Parameters other than survival curves have been compared for statistical differences by using the standard χ^2 method[14]

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Table 1 *Relationship of positive node rates to tumour size and site*

Parameters investigated	Tumours ≤2 cm Lateral	Tumours ≤2 cm Central	Tumours ≤2 cm Medial	Tumours >2 cm Lateral	Tumours >2 cm Central	Tumours >2 cm Medial
Total no	236	39	42	248	67	61
Low axillary node	80 (33 9)	13 (33·3)	10 (23·8)	139 (56)	33 (49·3)	23 (37·7)
Apical node	24 (10 2)	3 (7 7)	3 (7 1)	38 (15·3)	11 (16·4)	9 (14 8)
Internal mammary node	15 (6·4)	3 (7·7)	6 (14·3)	24 (9·7)	12 (17 9)	12 (19 7)

Values in parentheses are percentages

Table 2 *Lymph node stages and interrelationships of nodal status*

Stage	Low axillary node	Apical node	Internal mammary node	Total no.	
A	–	–	–	369 (53 2)	
B	+	–	–	191 (27 6)	
C	+	+	+	26	133 (19·2)
	+	+	–	56	
	+	–	+	25	
	–	+	+	1	
	–	+	–	5	
	–	–	+	20	
Total no	298 (+) (43 0)	88 (+) (12·7)	72 (+) (10·4)	693	

Values in parentheses are percentages

Results

The median follow-up period from initial treatment was 48 months (range 2–172 months). The median patient age at presentation was 56 years (range 27–70 years).

Positive node rates according to tumour size and site in the breast

Table 1 illustrates the relationships between node involvement and tumour site and size. Node positivity at each site increased significantly with increasing tumour size: for the apical node ($P<0{\cdot}02$), internal mammary node ($P<0{\cdot}05$), and for the low axillary node ($P<0{\cdot}001$). Lateral tumours overall were associated with low axillary node positivity ($P<0{\cdot}05$) compared with medially located tumours, which more frequently involved the internal mammary node ($P<0{\cdot}01$). There was no difference in the positive node rate between laterally and medially located tumours for the apical node. No significant difference could be found in the node positive rates of the apical node compared with the internal mammary node for centrally located tumours.

Interrelationships of nodal status according to lymph node stages

Table 2 shows the status of each node in relation to the two other nodes sampled and according to the present lymph node stages. The low axillary node was positive in 43·0 per cent, the apical node in 12·7 per cent and the internal mammary node in 10·4 per cent of cases. Out of a total of 72 positive internal mammary nodes only 20 were positive alone. In only six cases was the apical node positive without involvement of the low axillary node.

Survival according to node negative and node positive status

Figure 1 compares the survival curves of patients with all negative nodes (stage A) with patients who were all node positive (stages B and C). A highly significant difference ($P<0{\cdot}001$) between the two groups is illustrated.

Survival according to each node involved

In *Figure 2* survival curves for all cases with involvement of the low axillary node, the internal mammary node and the apical node are compared. A highly significant difference ($P<0{\cdot}001$) is seen between the groups. A significant difference ($P<0{\cdot}01$) can also be seen between the curves of all low axillary node positive and all apical node positive cases. No significant difference could be demonstrated between all the internal mammary node positive cases compared with either all the low axillary or apical node positive cases, implying that the internal mammary node does not contribute significantly more prognostic information. *Figure 2* illustrates that the prognostic value of the internal mammary node lies between the other two nodes sampled.

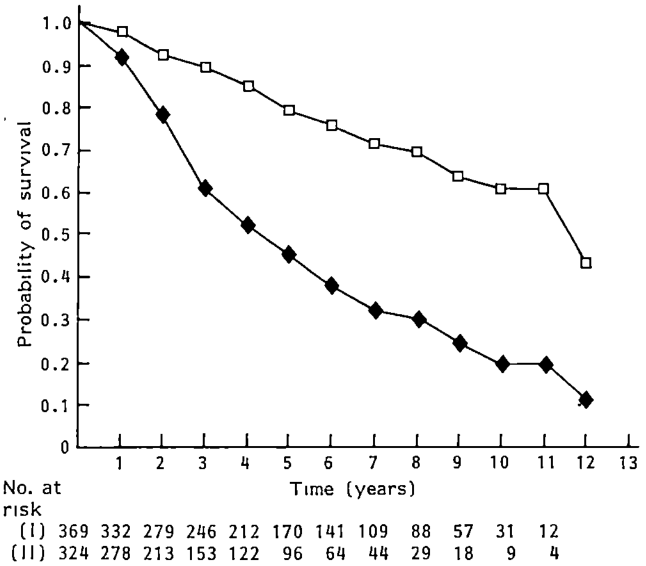
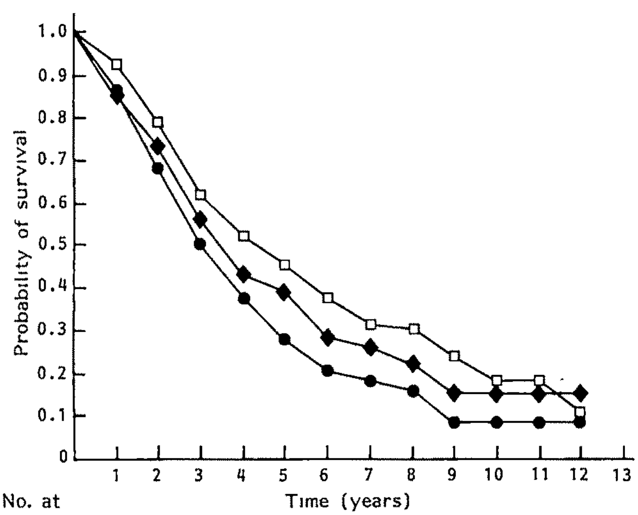


Figure 1 *Survival curves of patients with all nodes negative (□, I) compared with nodes positive (◆, II)* χ^2 *(1 d.f.)=94 42, P<0·001*

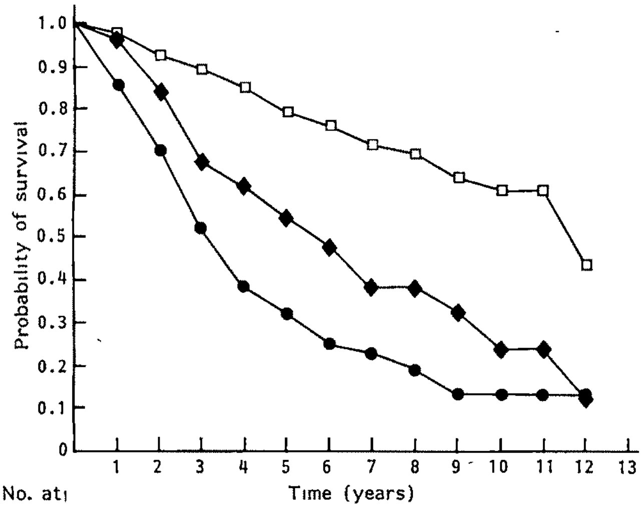
Survival according to present lymph node stages

The internal mammary node contributed 45 cases, the apical node 61 cases and both contributed 27 cases to the total group of 133 cases in stage C (19·2 per cent of all cases). The low



No. at risk											
(I)	298	257	196	143	114	90	60	40	27	16	7	4
(II)	72	60	48	34	25	19	11	7	3	2	2	1
(III)	88	71	51	34	23	15	9	8	5	2	1	1

Figure 2 *Survival curves of patients comparing low axillary node involvement (□, I), internal mammary node involvement (◆, II) and apical axillary node involvement (●, III)* χ^2 *(2 d.f.) = 28·71, P<0·001, I vs II (1 d.f.) = 2·25, P, n.s., I vs III (1 d.f.) = 8·09, P<0·01, II vs III (1 d.f.) = 2·25, P, n.s.*



No. at risk											
(I)	369	332	279	246	212	170	141	109	88	57	31	12
(II)	191	170	130	97	83	68	47	30	22	14	6	3
(III)	133	108	82	56	39	28	18	14	7	4	3	2

Figure 3 *Survival curves of patients in current Nottingham stages A (□, I), B (◆, II) and C (●, III) A, no nodes involved, B, low axillary node alone involved, C, internal mammary node or apical axillary node involvement alone or in any other combination.* χ^2 *(2 d.f.) = 392·37, P<0·001, I vs II (1 d.f.) = 45·41, P<0·001, I vs III (1 d.f.) = 114·89; P<0·001; II vs III (1 d.f.) = 15·17, P<0·001*

axillary node was positive together with either one or both of the high nodes in 107 cases.

Figure 3 shows survival according to present stages A, B and C. A highly significant difference exists between each stage compared with the other two.

Staging using alternative groupings

Considering *Figures 2* and *3* together, some of the internal mammary node positive cases ($n = 72$) could belong to stage B and some to stage C.

In *Figure 4* the prognostic information obtained from the low axillary and internal mammary nodes has been investigated as if a double node biopsy had been performed (apical node ignored). No significant difference is seen between low axillary positive alone and internal mammary positive alone, but if both nodes were positive together the prognosis deteriorated significantly.

When the survival curve of all cases where the low axillary and internal mammary nodes were positive simultaneously was compared with the curves of all apical node positive cases and all cases in stage C, no significant difference could be demonstrated between any of the curves when compared with each other (figure not shown).

Survival comparing double node with triple node biopsies

Taking the low axillary node as the constant factor, two double node biopsies may be performed using either the internal mammary or the apical node as the second node. Cases with the poorest prognosis in each of these situations occur when either of the high nodes is positive simultaneously with the low axillary node (*Figure 4*). In performing a triple node biopsy the same poor prognostic groups emerge but a group of cases where all three nodes are positive can be identified. No significant differences in prognosis could be demonstrated between double and triple node biopsies where all nodes sampled were positive (figure not illustrated). Comparing each of these three curves with the curve of the present stage C cases also demonstrated no significant difference (data not shown).

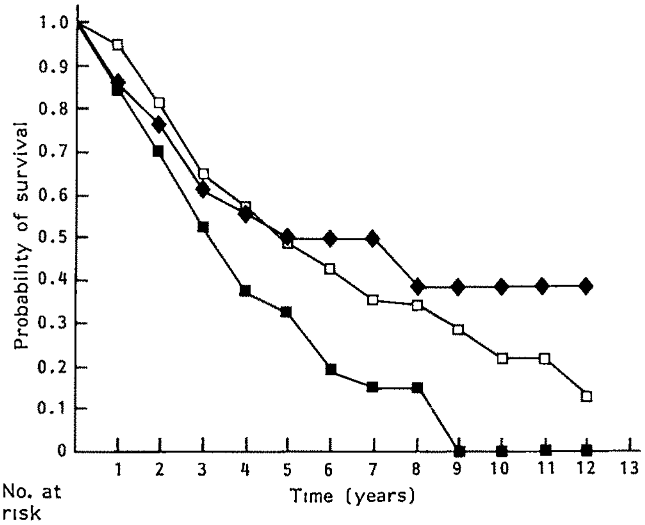
Influence on staging of missing a node during the sampling process

The internal mammary node was missed in 22 per cent ($n = 153$) of cases, the apical node in 18 per cent ($n = 126$) and the low axillary node in 3 per cent ($n = 20$) during the sampling process. To investigate the effect on staging, survival curves were constructed to compare 'true' stage A (all nodes identified but negative) with groups in stage A where one and two or more nodes had been missed, counting a missed node as negative No significant difference could be demonstrated between any of these groups (figure not illustrated).

Furthermore, to examine differences between 'true' stage B (low axillary node positive and the other two nodes identified but negative) and cases in which one or both the apical or internal mammary nodes were missed, comparison of survival curves showed no significant difference. These results indicate that missing a node in the sampling process had no significant effect on a patient's stage for either stage A or B.

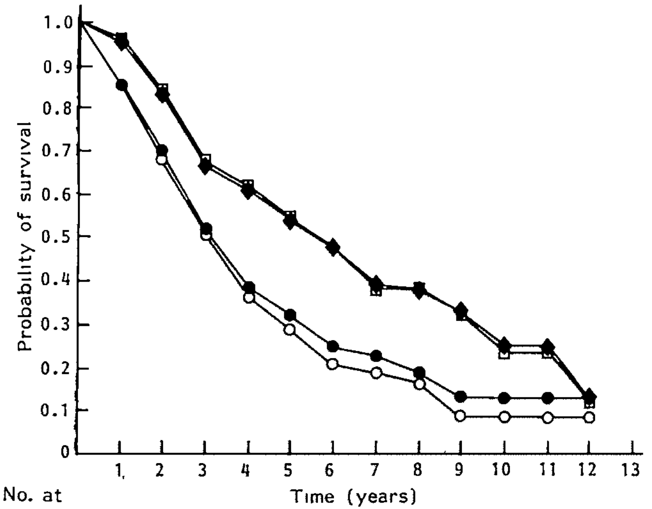
Effect of changing the current lymph node staging system

Since internal mammary node positivity alone carries the same



No. at risk											
(I)	247	215	163	119	97	77	54	37	26	16	7	4
(II)	21	18	16	11	10	8	6	5	3	2	2	0
(III)	51	42	32	24	17	13	6	3	1	0	0	0

Figure 4 *Survival curves of patients with low axillary node involvement alone (□, I), internal mammary node involvement alone (◆, II) and both low axillary and internal mammary nodes involved (■, III)* χ^2 *(2 d.f.) = 23·25, P<0·001, I vs II (1 d.f.) = 0·15, P, n.s., I vs III (1 d.f.) = 9·93, P<0·01, II vs III (1 d.f.) = 3·86, P<0·05*



No. at risk											
(I) 191	170	130	97	83	68	47	30	22	14	6	3
(II) 211	187	145	107	92	75	53	35	25	16	8	3
(III) 133	108	82	56	39	28	18	14	7	4	3	2
(IV) 113	91	67	47	32	23	13	10	5	2	1	1

Figure 5 *Survival curves of patients in old stage B (□, I) and old stage C (●, III) compared with new stage B (◆, II) and new stage C (○, IV) where the new stages are A, unchanged, B, lower axillary node alone or internal mammary node alone involved, C, patients with apical axillary node alone involved or in any other combination χ^2 (1 d.f.), I vs II=0 003, P, n s ; III vs IV=0 254, P, n.s.*

prognostic weight as low axillary node positivity alone (*Figure 4*), the current staging system could be redefined as follows:

Stage A: all nodes negative ($n=369$) – unchanged,

Stage B· low axillary or internal mammary node positive alone ($n=211$);

Stage C: all apical node positive cases plus cases with low axillary and internal mammary nodes positive simultaneously ($n=113$)

In *Figure 5* survival curves of possible new stages B and C are compared with old stages B and C and no significant differences are shown. Only 20 cases (axillary and internal mammary nodes positive) were transferred from the old stage C to the new stage B. *Figure 6* illustrates survival curves for the three 'new' stages.

Discussion

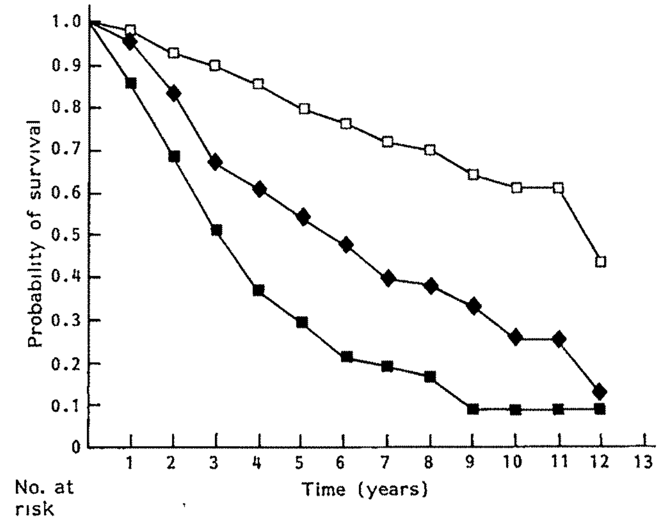
Complete and extensive dissection of both axillary[15,16] and internal mammary[17] lymph node chains does not influence survival benefit in early breast cancer. Sampling techniques can, however, provide prognostic information from lymph nodes while avoiding the complications of complete lymph node dissections[18] Sampling techniques may be inadequate anyway as quantification of the number of involved glands is not possible[19]. Most methods sample the lower axilla alone and omit lymph nodes in the higher levels of the axilla and internal mammary chain. The triple node biopsy technique samples both lateral and medial lymph node chains and the low axillary node, most often involved, contributes the most useful prognostic information about nodal status (*Table 2*). The additional information obtained by sampling the internal mammary node is not as important as the apical node (*Figure 2*). The patients with positive internal mammary nodes comprise two groups: a group in whom this node is positive alone with a prognostic weight similar to that where the low axillary node is positive alone ($n=20$; 3 per cent of all cases) and a group where it is positive together with the low axillary node, with the same poor prognosis as the group with involvement of the apical node ($n=51$; 7 per cent of all cases; *Figures 4* and *5*). Apical node positivity carries a very poor prognosis as expected from high level node involvement representing more extensive metastatic nodal disease. This is further illustrated by the fact that this node is usually involved together with the low axillary node (*Table 2*).

In this series the overall incidence of all internal mammary node positive cases was 10·4 per cent This node was positive alone in 28 per cent of these cases (20 out of 72 cases) and positive together with the low axillary node in 71 per cent of cases (51 out of 72 cases). In previous studies, with complete dissection of the internal mammary node chain, the overall incidence of all node positive cases varied between 19 and 35 per cent[9 20–22]. The incidence for internal mammary node positivity in these studies varied between 15 and 25 per cent and where it was positive with the lower axilla, between 75 and 85 per cent. Differences between these results and those of this series might be due to variations in tumour size and location in the breast. Only 15 per cent of the patients in this series had medially located tumours and 46 per cent were 2 cm or less in diameter. It is unlikely that many involved internal mammary nodes were missed during sampling as the data demonstrate that missed nodes had no effect on the survival curves of stages A and B. This implies that 'no node' is equivalent to a negative node provided a thorough search was made for the relevant node.

These results and those of others[9,20–22] demonstrate that tumour site relates to which nodal chain is involved (*Table 1*) and that double node biopsies give the same prognostic information as triple node biopsies. For medially located tumours, therefore, a double node biopsy including the internal mammary node and for laterally located tumours a double node biopsy including the apical node should give sufficient useful prognostic information to stage a patient. For centrally located tumours either apical or internal mammary biopsy must be added to low axillary biopsy.

Staging patients according to lymph node status (*Figures 3* and *6*) is a useful way of stratification into groups with differing prognoses. The more extensive the nodal involvement the worse the prognosis. This concept is used in the TNM staging system as recommended by the International Union against Cancer[23]. It is clinically easy to recognize a heavily involved axilla (N2 and N3 status) but difficult to differentiate between groups of patients with different prognostic outlooks when their lymph nodes are 'minimally' involved (N1b status). The sampling technique and staging method described clarifies this problem as it presents information from the low levels of the axilla and from the apical and internal mammary nodes

A triple node biopsy sampling technique, as in this study,



No. at risk											
(I) 369	332	279	246	212	170	141	109	88	57	31	12
(II) 211	187	145	107	92	75	53	35	25	16	8	3
(III) 113	91	67	47	32	23	13	10	5	2	1	1

Figure 6 *Survival curves of patients in new stages A (□, I), B (◆, II) and C (■, III). χ^2 (2 d.f.)=452 55, P<0·001, I vs II (1 d.f.)=48 32, P<0 001, I vs III (1 d.f.)=123 22, P<0·001, II vs III (1 d.f.)=19 50, P<0 001*

produces useful prognostic information on nodal status in early breast cancer, which can be used to stratify patients into different prognostic groups. This may allow better planning of systemic adjuvant treatment after primary management and may be helpful in deciding a follow-up regimen.

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Intact parathyroid hormone in primary hyperparathyroidism

In 49 patients with primary hyperparathyroidism, intact parathyroid hormone (PTH) was measured with a recently developed immunoradiometric assay, and midregional PTH fragments (sequence 44–68) were measured with an established radioimmunoassay technique. In 47 normal subjects, the concentration of intact PTH ranged from 2·0 to 6·8 pmol/l, and in 49 patients with primary hyperparathyroidism it ranged from 6·4 to 80·0 pmol/l. In contrast, midregional PTH fragments were normal in seven of 49 patients with primary hyperparathyroidism. In five healthy controls and in 12 patients with surgically confirmed primary hyperparathyroidism and serum calcium levels below 3·0 mmol/l, a rapid calcium loading test was performed. In healthy controls, intact PTH was in the low normal to subnormal range within 2·5–5·0 min, and had recovered within 15 min of calcium infusion. In patients with primary hyperparathyroidism, the calcium infusion also led to a 30–50 per cent decrease in intact PTH levels within 5·0–7·5 min after injection, with a slow recovery after 10–15 min. In six of the patients with only slightly elevated basal intact PTH, a suppression to the normal range was observed. In 24 patients (16 patients with a solitary adenoma and eight patients with four-gland hyperplasia) the intact PTH levels were followed intraoperatively during parathyroidectomy, revealing a significantly different rate of decline for single adenomas compared with hyperplasia during the first 15 min after removal of the primary enlarged gland. Intact PTH values remained constantly elevated in one patient with primary hyperparathyroidism and an unsuccessful neck exploration. These results confirm that (a) the measurement of intact PTH in patients with primary hyperparathyroidism is superior to the measurement of midregional fragments; (b) PTH secretion in primary hyperparathyroidism is not totally autonomous; and (c) intraoperative monitoring of intact PTH values could be used to monitor the success of surgery.

Keywords: Hyperparathyroidism, intact parathyroid hormone, calcium loading test

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The diagnosis of primary hyperparathyroidism still presents problems, such as the finding of normal parathyroid hormone (PTH) levels determined by radioimmunoassay, despite clinical evidence of the disease[1,2]. We have developed an immunoradiometric assay for intact PTH (sequence 1–84), as well as radioimmunoassays for sequences 44–68 and 53–84[3–5] Patients with primary hyperparathyroidism were evaluated by applying both the new immunoradiometric technique and the conventional midregional assays.

There have been a number of investigations on the suppressibility of PTH secretion in patients with primary hyperparathyroidism *in vivo* and *in vitro*[6–8]. In patients with only mild hypercalcaemia (2·6–3·0 mmol/l), calcium was infused for 3–4 h at a dose of 10 mg/kg body-weight, and PTH fragments in serum or urinary cyclic adenosine monophosphate were followed[8,9]. To increase the clinical applicability of this laborious and time-consuming conventional procedure, we tried to develop a rapid calcium infusion test aiming at an improved preoperative differential diagnosis of hypercalcaemia This rapid calcium infusion test was based on the assumption gained from previous experiments that the half-life of circulating intact PTH was less than 5 min.

Intraoperative monitoring of intact PTH may yield information on the half-life of the hormone in the circulation and may verify surgical success. Plasma levels were therefore determined in patients with adenomas and four-gland hyperplasia.

Patients and methods

Group of patients for PTH assay comparison

Forty-nine patients with primary hyperparathyroidism operated on in 1986 and 1987 at the Department of Surgery, University of Heidelberg, were investigated In all patients the diagnosis was confirmed by plasma calcium and PTH determination, in addition, phosphate, chloride and total protein, as well as albumin, in plasma were determined In 38 of the patients the clinical and laboratory diagnosis was confirmed by neck exploration; operation was deferred for various reasons in the remaining 11 patients.

Neck exploration included the exposure of all four parathyroid glands. Surgery was terminated if one normal and one abnormal parathyroid gland were identified by biopsy. If hyperplasia was encountered, all four glands were removed and one half-gland was transplanted to the forearm. Surgical outcome was defined as successful if the plasma calcium level fell to normal or subnormal values during the first 5 postoperative days PTH levels were also followed after operation.

Laboratory analysis

Determination of intact PTH was performed with an immunoradiometric assay[3] One antibody against the amino-terminal part of the hormone was produced in goats and conjugated to cellulose particles By means of these particles, intact PTH and amino-terminal fragments were extracted from plasma treated with ethylene diamine tetra-acetic acid (EDTA), and thus concentrated Another antibody against synthetic PTH (sequence 53–84) was produced in rabbits. This antibody was labelled indirectly and bound to the carboxy-terminal part of the hormone This assay showed no cross-reactivity with PTH fragments

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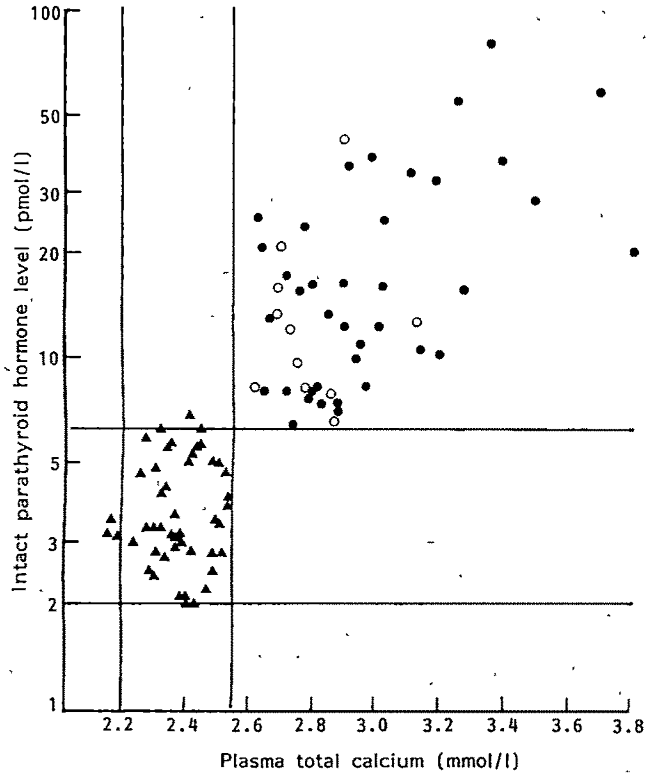

Figure 1 *Plasma total calcium and intact parathyroid hormone levels in 49 patients with primary hyperparathyroidism (●, surgically proven cases (38), ○, presumed cases (11)) and in 47 normal subjects (▲). The solid lines mark the limits of the normal ranges*

with the sequences 1–34, 1–44, 28–48, 39–84, 44–68 and 53–84. The minimum time required for the assay to be carried out is 64 h (Reference 3). All PTH peptides employed were of human origin isolated from adenomas or synthesized according to the human structure.

Determination of midregion PTH was performed with a conventional double-antibody radioimmunoassay for midregion PTH (sequence 44–68)[4].

Determination of calcium, phosphate, chloride, total protein and albumin were performed on the clinical chemistry multichannel selective analyser, Hitachi 737® (Boehringer Mannheim, Mannheim, FRG).

Rapid calcium infusion test

Calcium gluconate, 10 per cent (Sandoz, Nürnberg, FRG), 0·1 mg/kg body-weight, was injected intravenously over a period of 2·5 min. Before injection and every 2·5 min thereafter up to 15 min, 4 ml of peripheral blood was drawn in EDTA-containing monovettes (Sarstedt, Nümbrecht, FRG). The calcium infusion test was performed in 12 patients with primary hyperparathyroidism, in two other hypercalcaemic patients with an uncertain final diagnosis, and in five healthy controls. Informed consent was a prerequisite. The test was considered contraindicated if the hypercalcaemia exceeded 3·0 mmol/l (to prevent the induction of a hypercalcaemic crisis or calcium deposition) or if other risk factors such as cardiac arrhythmias precluded calcium administration.

Intraoperative blood sampling

Up to three 4 ml baseline samples were drawn from a peripheral vein at the beginning of neck exploration. The next sample was drawn when the adenoma was localized and ready for extirpation; at the same time as the supporting vessel of the gland was clamped. Every 2·5 min thereafter, up to 15 min, PTH levels were measured. This sequential PTH assay was performed in 24 patients, 16 with adenomas and eight with hyperplasia.

For all the studies, the blood was centrifuged within 2 h of collection from the patient and the EDTA-treated plasma was kept frozen at −30°C until PTH determination.

Results

PTH assay comparison

The relationship between plasma total calcium and PTH was examined in patients with primary hyperparathyroidism and in normal subjects. The patients had a mean(s.d.) plasma total calcium level of 2·94(0·27) mmol/l (range 2·62–3·80 mmol/l). There was only a weak correlation with calcium levels for both intact PTH (*Figure 1*) and midregional PTH (*Figure 2*) values in the patients with primary hyperparathyroidism. Some patients with mild hypercalcaemia showed high intact PTH values, whereas certain patients with moderate to severe hypercalcaemia had only a borderline increase in intact PTH.

Intact PTH values (*Figure 1*) discriminated between patients with primary hyperparathyroidism and healthy controls better than did midregional values (*Figure 2*). There existed only a moderate correlation between intact PTH and midregional fragments in patients with primary hyperparathyroidism (data not shown).

Rapid calcium infusion test

In five healthy volunteers, the baseline levels of intact PTH at the beginning of the loading test were within the normal range (2–6 pmol/l). Following calcium administration, the values fell to the low normal or subnormal range with a recovery occurring at about 15 min after infusion. Thus, a slight suppression of intact PTH secretion could be demonstrated in healthy subjects.

In all 12 patients with primary hyperparathyroidism, the calcium load led to a distinct decrease in circulating intact PTH during the study. None of the patients with primary hyperparathyroidism reached the initial value within 15 min of calcium infusion, although a partial recovery could be observed in all but two patients.

According to the initial baseline level of intact PTH, patients can be arbitrarily divided into two subgroups: (1) patients with initially high intact PTH levels (above 15 pmol/l) cannot be suppressed by the calcium infusion to the normal PTH range, even though a significant decrease occurs with a PTH minimum at 5–10 min after infusion followed by a slow recovery; (2) patients with only mild elevations of baseline PTH (6–15 pmol/l) show a similar PTH decrease with minimum levels at about

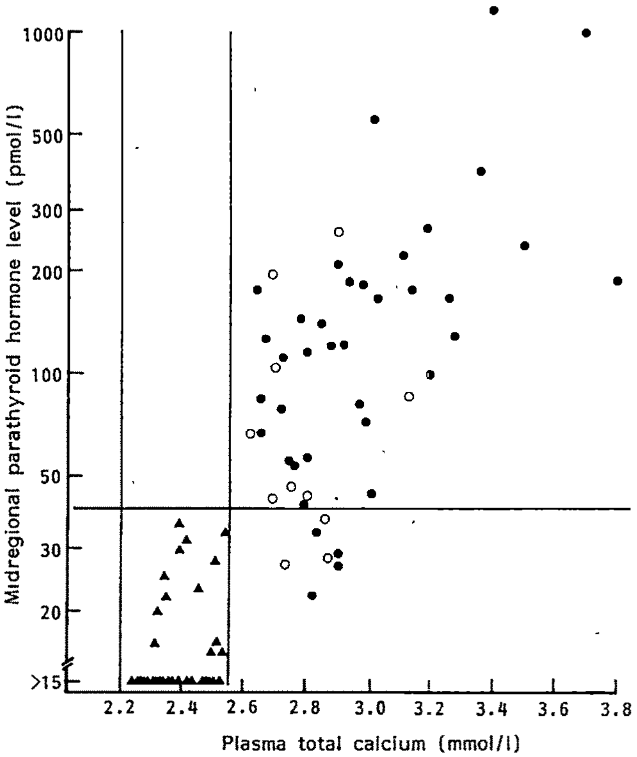

Figure 2 *Plasma total calcium and midregional parathyroid hormone levels (sequence 44–68) in 49 patients with primary hyperparathyroidism (●, surgically proven cases (38), ○, presumed cases (11)) and in 47 normal subjects (▲). The solid lines mark the limits of the normal ranges*

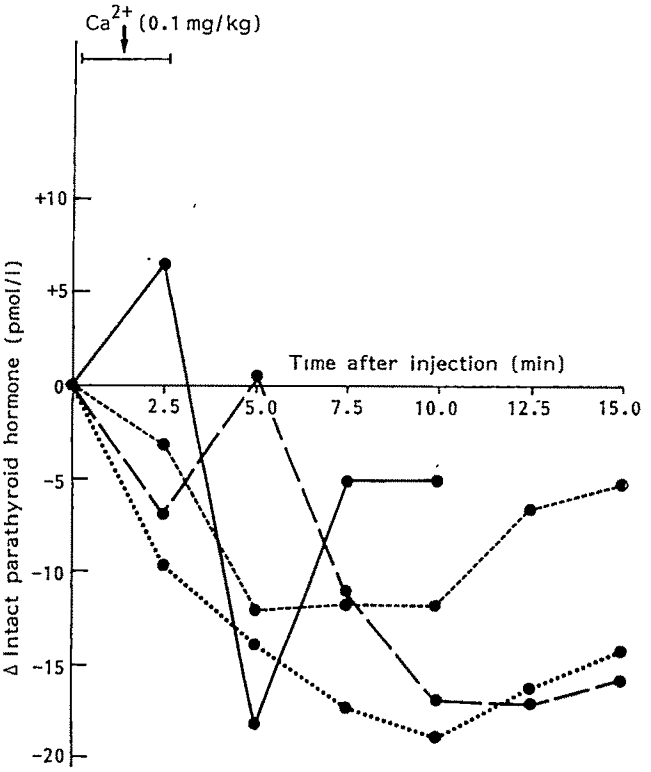

Figure 3 *Levels of intact parathyroid hormone in four of 12 patients with primary hyperparathyroidism with baseline parathyroid hormone levels above 15 pmol/l, expressed as the change from the initial value during the rapid calcium infusion test*

5–10 min after injection, and levels in these patients can even be suppressed to the high normal range. In four of the latter six patients, intact PTH recovered at about 15 min, two other patients remaining partially suppressed. To emphasize the differences between the subgroups, the data are presented as changes from the original PTH values (*Figures 3* and *4*).

In two additional patients with hypercalcaemia of uncertain origin, the calcium loading test was also performed (data not shown). In one of these patients with hypercalcaemia of 2·8–3·0 mmol/l, the preoperative level of intact PTH was normal. The diagnosis of primary hyperparathyroidism was suggested by plasma calcium elevations, low phosphate and a history of kidney stones. Surgery (including metachronous sternotomy to exclude an ectopic adenoma) was non-revealing, and no adenoma was found. In this patient, the rapid calcium infusion test showed the same pattern as that observed for healthy controls, with a baseline PTH level of 3·1 pmol/l and a decrease to about 2·0 pmol/l 15 min after calcium infusion Further follow-up did not confirm the existence of primary hyperparathyroidism. In a second patient, primary hyperparathyroidism was suggested by the clinical data, but the operation was deferred because of an acute cerebral ischaemia and deterioration of the patient's general condition. A previously performed calcium loading test showed an initial intact PTH level of 16·8 pmol/l which dropped to 9·0 pmol/l at 7·5 min and recovered to 13 pmol/l at 15 min, this course being highly suspicious of the existence of primary hyperparathyroidism.

Intraoperative intact PTH monitoring

In 16 patients with a solitary adenoma and eight patients with hyperplasia of the parathyroid glands, as well as in one additional patient with primary hyperparathyroidism who underwent an unsuccessful neck exploration, intact PTH levels were followed during parathyroidectomy A rapid decrease of the elevated intact PTH values was seen in all 16 patients with a single adenoma. normal levels were reached 15 min after clamping and removal of the adenoma (*Figure 5*).

In six of 16 adenoma patients, a greater than 50 per cent decrease in circulating intact PTH was observed between the baseline level and the sample drawn at the time when the adenoma was clamped and removed; this may reflect the preceding devascularization of the adenoma by the operative exploration and manipulation of the enlarged gland.

By contrast, the rate of decline was significantly slower in patients with hyperplasia (*Figure 6*). None of the eight patients reached normal values within the observation period. The increase in the serum half-life of intact PTH, varying from 5 to 15 min, reflects the progressive removal of hyperfunctioning parathyroid tissue. The difference in the decline curves of adenomas *versus* hyperplastic glands was statistically significant at $P<0{\cdot}01$ (Student's *t* test).

In one patient with primary hyperparathyroidism, an enlarged gland could not be localized during the first operation. Intraoperative intact PTH monitoring showed a persistent elevation of peripheral hormone levels during the entire exploration. Re-exploration because of persistent severe hypercalcaemia was performed 10 months later revealing an adenoma in the ventral mediastinum adjacent to the thymus.

Discussion

During the past decade, the determination of serum PTH levels has become a major diagnostic tool in the differential diagnosis of hypercalcaemia[10]. By use of conventional assay techniques with antibodies directed against amino-terminal or carboxy-terminal fragments of the PTH molecule, a considerable overlap between normal subjects and hyperparathyroid patients has been found due to false positive and false negative measurements[8,10,11]. This phenomenon can be attributed to free circulation of biologically inactive metabolic products of the intact hormone: It has been shown that only about

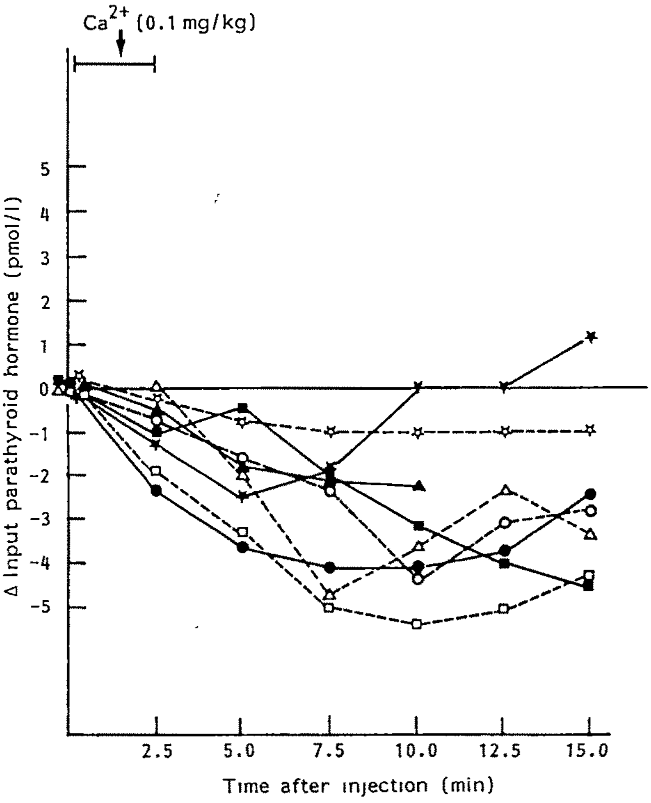

Figure 4 *Levels of intact parathyroid hormone in eight of 12 patients with primary hyperparathyroidism with baseline parathyroid hormone levels between 6 and 15 pmol/l, expressed as the change from the initial value during the rapid calcium infusion test*

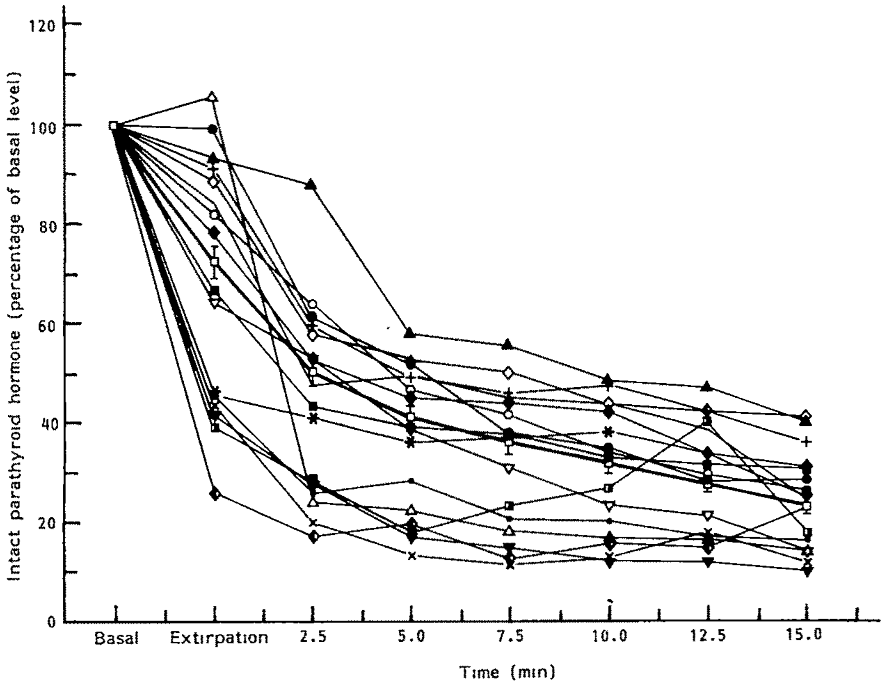

Figure 5 *Intraoperative intact parathyroid hormone (PTH) levelsfollowed over 15 min in 16 patients (P1–P16) with a single parathyroid gland adenoma The results are presented as the percentage of the basal PTH value. (Basal, PTH value at the beginning of the operation, extirpation, PTH value at the time when the enlarged gland was clamped and removed.)*

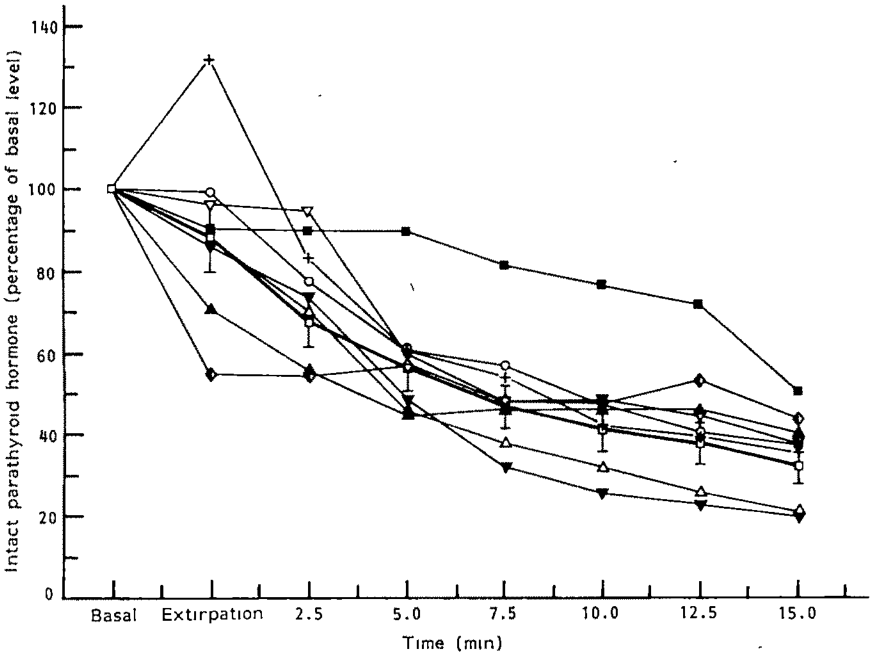

Figure 6 *Intraoperative intact parathyroid hormone (PTH) levels followed over 15 min in eight patients (P1–P8) with four hyperplastic parathyroid glands. The results are presented as the percentage of the basal PTHvalue (Basal, PTH value at the beginning of the operation, extirpation, PTH value at the time when the enlarged gland was clamped and removed)*

15 per cent of the total immunoreactive PTH exhibits biological activity, as measured by stimulation of the rat kidney adenyl cyclase[12].

The recent development of a new extracting two-site immunoradiometric assay in our own laboratory has made the determination of the intact human PTH possible This modified assay system allows an almost complete distinction between normal subjects and patients with primary hyperparathyroidism, as has been shown above and by earlier reports from our group[13] and by other authors[9,14,15]. In spite of slightly differing techniques to measure intact PTH, the clinical relevance is comparable for the assays mentioned. This is further reflected by the similarity of their normal range and their ability to discriminate between tumour hypercalcaemia and primary hyperparathyroidism By the use of monoclonal antibodies, the assay described by Brown *et al.*[14] can be performed within 5 h, but it is slightly less sensitive than our procedure In contrast to many conventional radioimmunoassays for PTH fragments, the enhanced sensitivity of two-site assays allows PTH measurements in the subnormal range, which is an important prerequisite for testing the suppressibility of PTH secretion in normal subjects

As has been reported earlier, intact PTH is removed from the circulation within minutes due to rapid uptake and cleavage by the liver[16]. This phenomenon could be used to follow the fate of the intact hormone during surgery for hyperparathyroidism as well as during a rapid calcium loading test.

The application of an oral or intravenous calcium load to test for a hyperfunctioning parathyroid gland is a known, established technique in endocrinology[17]. In the rapid calcium infusion test described above, calcium was administered intravenously during a very short time interval (2·5 min) to follow the immediate response of the parathyroid tissue. In control subjects, PTH serum levels fell to low normal or subnormal values shortly after injection and recovered slowly during the examination period, reflecting a clear suppressibility of the hormone excretion. Another possible explanation for this decrease would be an enhancement of the degradation by the liver.

In parallel to the normal healthy controls, PTH levels also decreased after calcium administration in the hyperparathyroid patients This behaviour was particularly marked in patients with high basal levels of PTH and contradicts the thesis of total autonomy in the hyperparathyroid state. A similar *in vivo* observation in a patient with primary hyperparathyroidism has been published by another group[15]. This lack of autonomy has been reported by other investigators *in vitro*[6,7,18] using dispersed cells from adenomatous, hyperplastic and normal parathyroid tissue. Their results point to a direct effect of calcium on hormone release. In contrast, no significant changes in PTH levels could be measured in analogue experiments *in vivo* when amino-terminal or carboxy-terminal assays were used[8]. By use of an assay for intact PTH, our investigations could reproduce the *in vitro* data reported on calcium suppression of parathyroid adenomas. Even though the results do not yield additional diagnostic information for the respective patients, they nevertheless provide further insight into the pathophysiology under *in vivo* conditions and support the known *in vitro* studies. Our initial intention also to perform this calcium suppression test on patients with hyperplasia, in order to detect potential differences compared with adenomas, was rendered impossible by the fact that none of the patients presenting with hyperplasia had basal calcium values below 3 0 mmol/l, which we regard as a contraindication to the test. In contrast to the suppression test described here, calcitonin stimulation of PTH release has recently been reported to cause a differential increase in secretory activity of adenomas compared with hyperplastic glands in the *in vivo* situation[19].

The follow-up of intact PTH levels during surgery for adenoma or hyperplastic glands reveals a very rapid decrease of the intact hormone in the peripheral circulation, thus confirming the success of the operation The observed difference between patients with adenoma *versus* hyperplasia in the postoperative decline of intact PTH levels may be attributed to the stepwise removal of the hyperfunctioning tissue in hyperplasia. Eventually, hyperplasia misdiagnosed as a single adenoma may later be disclosed by the difference in the PTH decline curve. From data in patients with an adenoma, a serum half-life of intact PTH of between 2·5 and 7·5 min can be derived. In contrast, the decline of the carboxy-terminal hormone fragments occurs at a much slower rate, lasting about 24 h or more[20]. Thus, the decay in postoperative intact hormone levels can be considered to be of importance for the differential diagnosis of recurrent or persistent hyperparathyroidism, for instance in the case of more than one adenoma, ectopic adenoma or reoperations. This is of particular importance for those cases in which a temporary postoperative calcium decrease suggests successful surgery in spite of persistent disease. Similar observations have been made by other authors; in addition, in the case of recurrence, the PTH values can be elevated even before the occurrence of hypercalcaemia[21].

If in the future a rapid intraoperative assay for intact PTH is developed it would find a valuable clinical role.

Acknowledgements

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Synthesis of prostaglandins I_2 and E_2 by the canine gallbladder *in vitro*: studies using a new incubation chamber

*Using a specially designed incubation chamber, differential synthesis and the response to added arachidonic acid (25 mM) and L-α-phosphatidylcholine (LAP; 2 mM) was quantified in gallbladders from male and female dogs. Prostaglandin I_2 (PGI_2) was the predominant prostanoid synthesized, and tissues from females produced much more PGI_2 under basal conditions than did gallbladders harvested from male dogs. Addition of arachidonic acid stimulated PGI_2 synthesis by almost 100 per cent. Arachidonate-stimulated mucosal and serosal production of PGI_2 were (mean(s.e.m.)) comparable, 343(178) and 375(89) pg/cm²/min, respectively. Gallbladders from female animals synthesized significantly more PGI_2 than did tissue from males. Indomethacin inhibited PGI_2 synthesis in a dose–*response manner; at *7×10^{-5} M, prostanoid synthesis was inhibited by >80 per cent. Arachidonic acid did not stimulate prostaglandin E_2 (PGE_2) production by gallbladder tissue. LAP similarly stimulated PGI_2 biosynthesis, but in contrast to the effect of arachidonic acid, the effect was significantly greater in the serosa than the mucosa, 355(107) and 213(59) pg/cm²/min, respectively. LAP also stimulated PGE_2 biosynthesis by the canine gallbladder in a pattern very similar to that of PGI_2. Based on the differences in response to the two agents added, we conclude that arachidonic acid and L-α-phosphatidylcholine stimulate prostaglandin biosynthesis via independent pathways. We advocate the use of the incubation chamber for the assessment of prostanoid biosynthesis by the gallbladder* in vitro.

Keywords: Canine gallbladder, prostaglandin synthesis

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A number of recent studies have documented prostaglandin synthesis by the gallbladder[1–4]. While the physiological role of prostanoids in gallbladder function is not known, these compounds may function to stimulate smooth muscle contractility[5,6], inhibit solute-dependent fluid absorption[7], and/or augment mucus production[8]. Abnormalities or imbalances in one or more of these properties may participate in the pathophysiology of gallbladder disease. Kaminsky and colleagues have recently demonstrated that gallbladders from patients with cholelithiasis synthesize more prostacyclin than do normal gallbladders[9].

To date, the published studies characterizing prostaglandin biosynthesis by the gallbladder have used either tissue homogenates[2] or full thickness explants[4,8]. Little is known about the distribution or prostanoids within the gallbladder wall. Since the incidence of biliary tract disease is two to threefold higher in females than males, it is important to determine the sex-specific rates of prostaglandin synthesis. Since prostacyclin and prostaglandin E (PGE) have both been implicated in inflammatory processes[2,3], data on the relative concentrations of these prostanoids may be of importance in explaining pathophysiological events related to biliary tract inflammatory disease. Finally, dissection of the specific roles of phospholipase and cyclo-oxygenase in biliary eicosanoid synthesis may provide an approach to the therapy of gallbladder disease.

The major objective of this study was to characterize the *in vitro* synthesis of a number of eicosanoids by the canine gallbladder using a specially designed incubation chamber. Utilizing this new technique, we have quantified the differential prostanoid responses of gallbladder slices to L-α-phosphatidylcholine (LAP) and arachidonic acid by comparing tissue from females with tissue from males, synthesis rates in the serosa *versus* the mucosa, and the relative synthesis of prostacyclin and PGE.

Materials and methods

Fasting adult mongrel dogs ($n = 60$) of both sexes were anaesthetized (sodium pentobarbitol, 30 mg/kg) and maintained on a Harvard respirator (So. Natick, Massachusetts, USA) on room air at 15 breaths/min. The gallbladders were removed through a midline abdominal incision and the animals were killed. The gallbladders were opened longitudinally and placed in Hepes buffer, pH 7.35, in a double-jacketed water bath through which a mixture of 95 per cent oxygen and 5 per cent carbon dioxide was constantly bubbled at 37°C. Full-thickness sections were prepared after exactly 30 min and placed in a special chamber, designed and produced in our laboratory, which permitted simultaneous, independent incubation of 1.0 cm² segments of the serosal and mucosal surfaces (*Figure 1*). The chambers contained four separate cells, each having two distinct access portals as displayed in the diagram.

The sequence of incubations was identical in all experiments and consisted of five study periods, each of 6 min. The first two periods were for measurement of spontaneous prostaglandin production. During these periods, oxygenated Hepes buffer (2 ml) was used as the incubation solution. The test agents were added for the duration of the third period and then removed by aspiration without rinsing (using ^{3}H-arachidonic acid, it was documented that >95 per cent of the eicosatetraenoic acid was removed by simple aspiration). The experiments were concluded with two additional periods of spontaneous control incubation. The chambers were kept in an incubator at 37°C for each 6-min period. After each period, the medium was removed,

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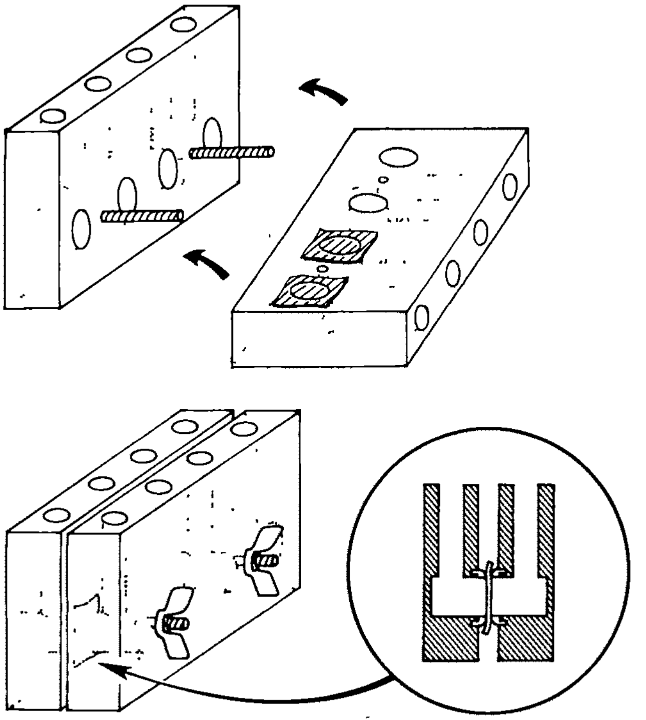

Figure 1 *Diagram of incubation chamber*

added to 0·01 ml/ml of buffer containing 25 mmol acetylsalicylic acid and the samples immediately frozen at −20°C for subsequent prostanoid radioimmunoassay. Arachidonic acid (Sigma Chemical Co., St Louis, Missouri, USA) was initially dissolved in ethanol and diluted to the required concentrations with the incubation medium (Hepes); the final alcohol concentration was always <0·01 per cent. LAP (97 per cent pure containing 0·1 per cent lysophosphatidylcholine and no arachidonic acid, Sigma Chemical Co.) was prepared for use by dissolving 100 mg in hexane. The hexane was blown off in air and concentrations of 2 mM were prepared by dilution in buffer. The hexane content was always <0·1 per cent. At these concentrations, the solvents did not interfere with the assays[10]. The control experiments were conducted using the incubation medium for all five periods. Following the final period, all tissue samples were recovered from chambers and fixed in formalin/glutaraldehyde for light microscopic analysis. Histologically, all tissue specimens were normal at the time of termination of the study. In order to document the viability of the preparations further, after completion of the study, an additional cycle of six periods of testing was performed in gallbladders from several animals. These tissues responded to arachidonic acid in the second cycle as they did in the first.

Tissue slices were incubated ($n = 3$) for 60 min at 37°C with 50 nmol ^{3}H-arachidonic acid (New England Nuclear Co., Boston, Massachusetts, USA) in 2 ml of the standard incubation mixture. At 6-min intervals over the 60 min period, 0·1 ml aliquots were removed from each well and 0·1 ml of fresh control medium added. After 60 min, the sections of gallbladder were precisely trimmed to the actual area which had been exposed, blotted, weighed, and dissolved in 10 ml of 5N NaOH. Of the resultant fluid 1 ml was then added to toluene-based scintillation fluid (RPI Complete Counting Cocktail, 3a70 NT, RPI Co., Prospect, Illinois, USA). Using this technique it was established that the uptake of ^{3}H-arachidonic acid by mucosa and serosa were identical, representing (mean(s.e.m.)) 0·6(0·8) per cent at 6 min and 1·6(0·2) per cent at 60 min. In alternative experiments, the ^{3}H-arachidonate was placed on either the mucosal or serosal side, the opposite chambers filled with control Hepes medium. No radioactivity crossed from serosa to mucosa or from mucosa to serosa.

Arachidonic acid was added during period 3 as one of the test solutions (50 nmol/2 ml or 25 mM) in 12 experiments to document the role of cyclo-oxygenase. Similarly, LAP (2 mM) was added during period 3 as an alternative test solution in 14 experiments to document the role of phospholipase. Experiments were conducted identically to those using arachidonic acid. Indomethacin (Sigma Chemical Co.) was added at concentrations of 7×10^{-5}, $3·5 \times 10^{-5}$, 7×10^{-6}, 7×10^{-7} and 7×10^{-8} M ($n = 5$ each) to document that the synthesis of prostanoids was appropriately inhibitable.

Prostaglandin I_2 (PGI_2, as its stable hydrolysis product, 6-keto-$PGF_{1\alpha}$) and prostaglandin E_2 (PGE_2) were assayed using specific homologous antibodies in radioimmunoassay[10]. The standard curves were constructed using log–logit analysis. Separate blanks were prepared for each sample and analyses were performed in duplicate. Maximal sensitivity of the assay (the limit of detection) for 6-keto-$PGF_{1\alpha}$ was 25 pg/ml, with 50 per cent inhibition of binding produced by 100 pg/0·1 ml. The limit of detection of PGE_2 was 10 pg/ml, with 50 pg/0·1 ml causing 50 per cent inhibition of binding. The PGE_2 antiserum had 100 per cent cross-reactivity with PGE_1 and hence, results reflect total PGE activity. Results are expressed as synthesis rates, picograms of prostanoid/cm^2/min.

Arachidonic acid and LAP caused slight interference in the PGE (but not the 6-keto-$PGF_{1\alpha}$) assay, shifting the calibration curve minimally to the right. Hence, all PGE assays for period 3 were conducted after the addition of either 25 nmol arachidonic acid/ml of assay buffer or 2 mM phosphatidylcholine, respectively, to all tubes to quench the non-specific interference. Studies using ^{3}H-arachidonic acid demonstrated that <5 per cent of the arachidonate remained in the well after emptying of the chamber (i.e. in period 4, the period after arachidonate was added). None the less, to assure the lack of arachidonate-induced interference, relevant radioimmunoassays for period 4 were performed after adding 1·25 nmol of arachidonic acid (5 per cent of the period 3 concentration) to 1 ml of the incubation mixture. Since virtually all the phosphatidylcholine was aspirated at the conclusion of period 3, samples from periods 1, 2, 4 and 5 were assayed using buffer without added phosphatidylcholine.

Data are presented as mean(s.e.m.). Since the data for periods 1 and 2 were virtually identical, they were averaged (as basals), to simplify the presentation of the data. Statistical comparisons of the conditions using the same tissue segments were performed using a *t* test for paired data; all other statistical analyses utilized a *t* test for unpaired data. *P* values of less than or equal to 0·05 were considered significant.

Results

Basal synthesis of eicosanoids

Under basal conditions, the gallbladder slices synthesized significant amounts of prostaglandins. Baseline secretory rates of PGI_2 and PGE averaged 1612(225) and 300(50) pg/cm^2/min, respectively. While gallbladders from 13 female animals synthesized more PGI_2 than did those from 13 males (2029(349) *versus* 1196(225) pg/cm^2/min), this difference was not significantly different ($P > 0·05$). Gallbladder PGE synthesis rates were similar in females and males (375(80) and 375(49) pg/cm^2/min, respectively). In contrast, rates of synthesis of thromboxane A_2 were significantly slower, 101(17) pg/cm^2/min of thromboxane B_2; $n = 3$; $P < 0·05$.

As shown in *Figure 2*, indomethacin inhibited PGI_2 synthesis in a dose-dependent fashion. At 7×10^{-5} M, the inhibition was more than 80 per cent complete, documenting the authenticity of the synthesized prostaglandins.

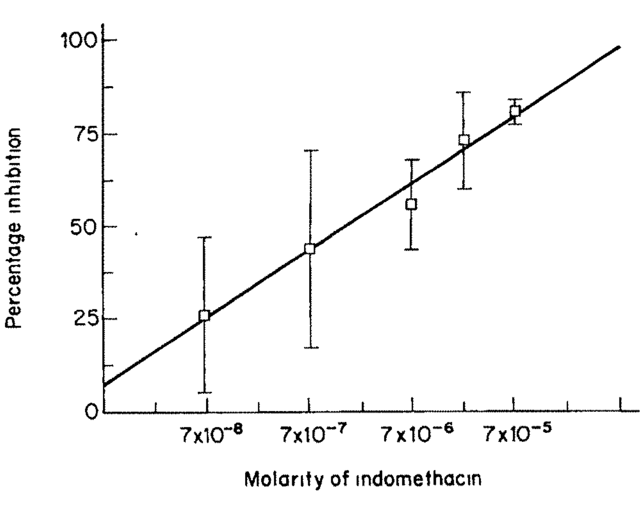

Figure 2 *Dose*–response inhibition of PGI_2 *synthesis by indomethacin* (7×10^{-8} *to* 7×10^{-5} *M). For these studies* ($n = 5$ *each), indomethacin, or the control diluent, was added for 6 min and then removed*

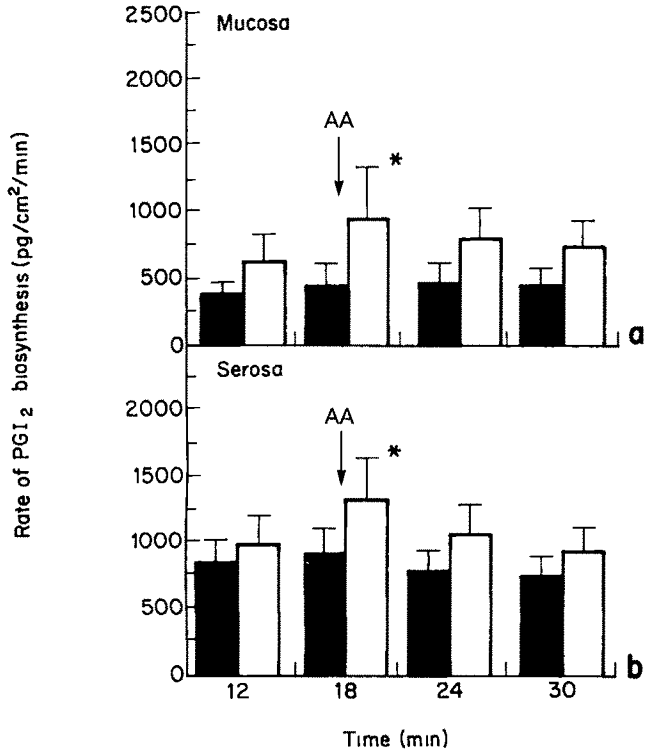

Figure 3 *Prestimulation and poststimulation synthesis rates of PGI$_2$ (6-keto-PGF$_{1\alpha}$) for the mucosa (a) and serosa (b) of control gallbladders (■) and those stimulated with arachidonic acid (□). Arachidonic acid (25 mM) was added for 6 min (at the arrow) and then removed. Data represent mean(s.e.m.) of the 6 min before, the 6-min stimulation period, and two recovery periods in 12 animals (males and females). In control studies, diluent was added instead of arachidonic acid and the studies otherwise performed identically The arachidonic acid caused a significant (*$P<0\cdot05$) increase in the mean rate of PGI$_2$ biosynthesis by both tissues*

Arachidonate-stimulated eicosanoid synthesis

Addition of 25 mM arachidonic acid to the incubation chambers augmented rates of prostacyclin biosynthesis As documented in *Figure 3*, the arachidonate stimulated PGI$_2$ synthesis (measured as its stable metabolite, 6-keto-PGF$_{1\alpha}$) by both the mucosal and serosal surfaces of the 12 gallbladders studied This effect was quantitatively similar in both surfaces of the gallbladder; when corrected for basal biosynthesis, the mean peak rates of PGI$_2$ production by mucosa and serosa were 343(178) and 375(89) pg/cm^2/min, respectively ($P>0\cdot05$)

The prostacyclin stimulatory effect of arachidonic acid was much more pronounced in the gallbladders from six female animals than in tissue from an equal number of males. As demonstrated in *Figure 4*, the increase in PGI$_2$ biosynthesis during the arachidonic acid period was greater in incubation studies using gallbladder slices from female animals than in those from males. When corrected for baseline eicosanoid biosynthesis, the mean peak rates of PGI$_2$ production by female gallbladder serosa (504(134) pg/cm^2/min) and mucosa (575(357) pg/cm^2/min) were significantly greater than comparable data from gallbladder tissue from male animals (243(111) and 112(60) pg/cm^2/min, respectively).

There were no differences in the biosynthetic abilities of different regions of the gallbladder. Rates of arachidonic acid-stimulated PGI$_2$ synthesis averaged 2336(511) ($n=20$), 1885(457) ($n=20$) and 1912(463) pg/cm^2/min ($n=10$) for the fundus, body and neck, respectively.

In contrast to the effects of prostacyclin, addition of arachidonic acid to the incubation chambers did not increase rates of biosynthesis of PGE$_2$ by either mucosal or serosal slices derived from female or male animals (data not shown).

Phosphatidylcholine-stimulated eicosanoid synthesis

Phosphatidylcholine (LAP) at 2 mM (but not 1 mM) was an effective stimulator of endogeneous prostacyclin biosynthesis. As shown in *Figure 5*, in which 14 gallbladders were studied (seven each of male and female), the addition of 2 mM LAP

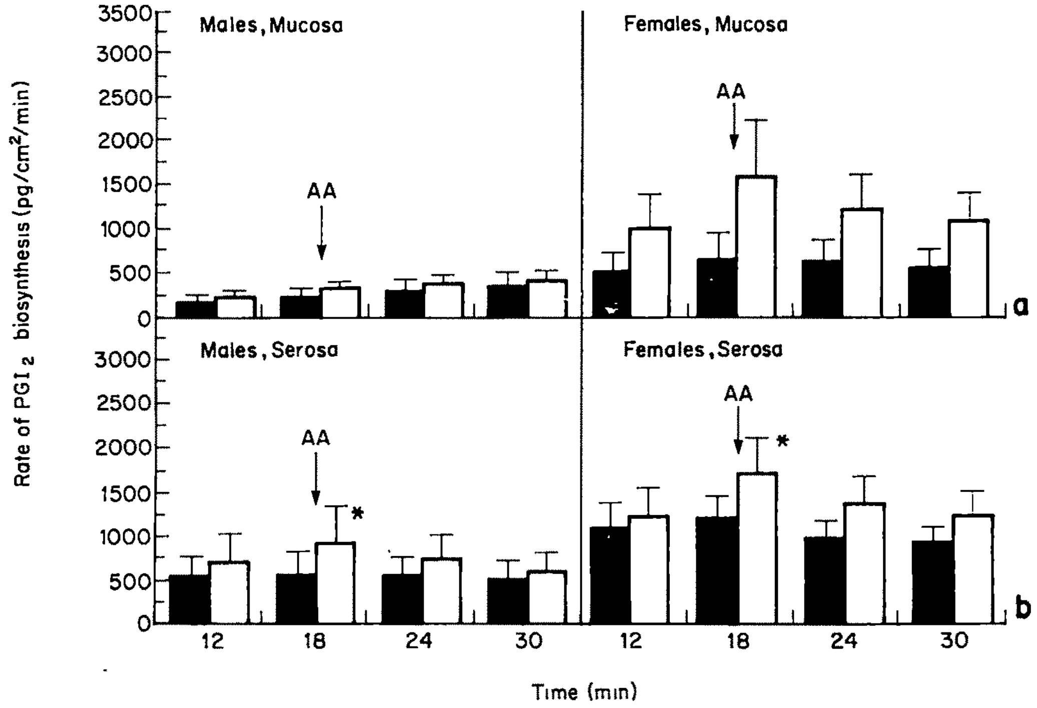

Figure 4 *The effect of arachidonic acid on PGI$_2$ biosynthesis by mucosal (a) and serosal (b) surfaces of the gallbladder from 12 dogs (six males and six females) Arachidonic acid (25 mM) was added for 6 min (at the arrows) and then removed. ■, control studies; □, arachidonic acid studies. Data at 12 min represent the average basal data from the first two 6-min control periods The mean arachidonic acid stimulated PGI synthesis rates by serosa from gallbladders from male and female animals were significantly (*$P<0\cdot05$) greater than those in control studies*

augmented PGI_2 biosynthesis (as measured by 6-keto-$PGF_{1\alpha}$) in both the mucosa and serosa. When the data were corrected for baseline PGI_2 biosynthesis, it became clear that the effect of LAP was much more pronounced in the serosa than the mucosa. In fact, the increase in the mean PGI_2 secretory rate (peak minus basal) for the serosa (355)107) pg/cm^2/min) was greater than that for the mucosa (213(59) pg/cm^2/min).

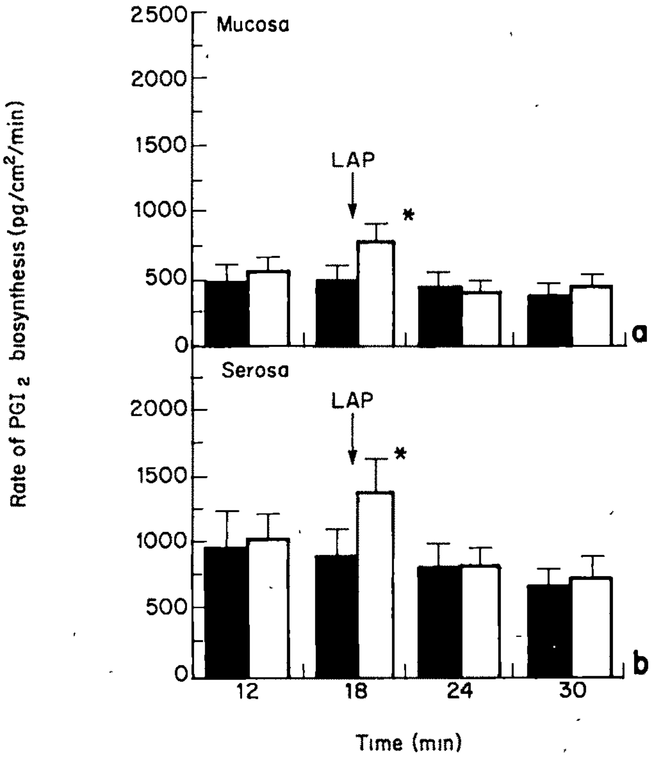

Figure 5 *The effect of LAP on PGI_2 biosynthesis by mucosa (a) and serosal (b) surfaces of the gallbladder from 14 dogs (seven males, seven females).* ■, *control studies,* □, *LAP studies. Data at 12 min represent the average data from the first two basal 6-min periods* *$P < 0.05$

Similarly, phosphatidylcholine was a more effective stimulator of prostacyclin biosynthesis by gallbladders from female animals than those from males. In gallbladders from seven male dogs (*Figure 6*), the LAP-induced increase in PGI_2 biosynthesis was not statistically significant ($P > 0.05$) in either the mucosal or serosal surfaces. The specific increases in the prostacyclin secretory rate (peak minus basal) in the mucosa (108(80) pg/cm^2/min) and serosa (120(91) pg/cm^2/min) were similar. In contrast, in seven gallbladders from female dogs, LAP significantly ($P < 0.005$) stimulated endogenous PGI_2 biosynthesis However, the stimulated rate of prostacyclin synthesis (peak minus basal) for the serosa (603(151) pg/cm^2/min) was greater than that of the mucosa (307(62) pg/cm^2/min).

Very similar observations were made regarding the biosynthesis of PGE. As with PGI_2, the rate of LAP-stimulated synthesis of PGE was greater in the serosa than in the mucosa. In fact, as shown in *Figure 7*, the data which include seven male and seven female dog gallbladders, the rate of endogeneous PGE biosynthesis was significantly stimulated only in the serosa. The mean increase in serosal secretion, 122(48) pg/cm^2/min, represented virtually a 100 per cent increase over basal. Similarly, the eicosanoid response to LAP was also sex-related. While there was no significant phosphatidylcholine-induced change in the rate of PGE secretion in males (in either mucosa or serosa; data not shown), gallbladders obtained from seven female dogs responded to the addition of LAP and this effect was restricted to the serosal surface (*Figure 8*). The increased serosal PGE secretory rate above basal (173(85) pg/cm^2/min) was statistically significant ($P < 0.05$).

Discussion

Characterization of prostaglandin synthesis *in vivo* is beset with difficulties owing to the instability and short half-lives of these compounds. Once formed, prostaglandins are immediately released from their site of synthesis, as demonstrated for the gallbladder by LaMorte *et al.*[11]. To solve this analytical problem, we have developed an *in vitro* model which seems to provide an accurate method for quantification of prostanoid synthesis by the gallbladder. One purpose of this study was to validate this new model using 1·0 cm^2 segments of canine

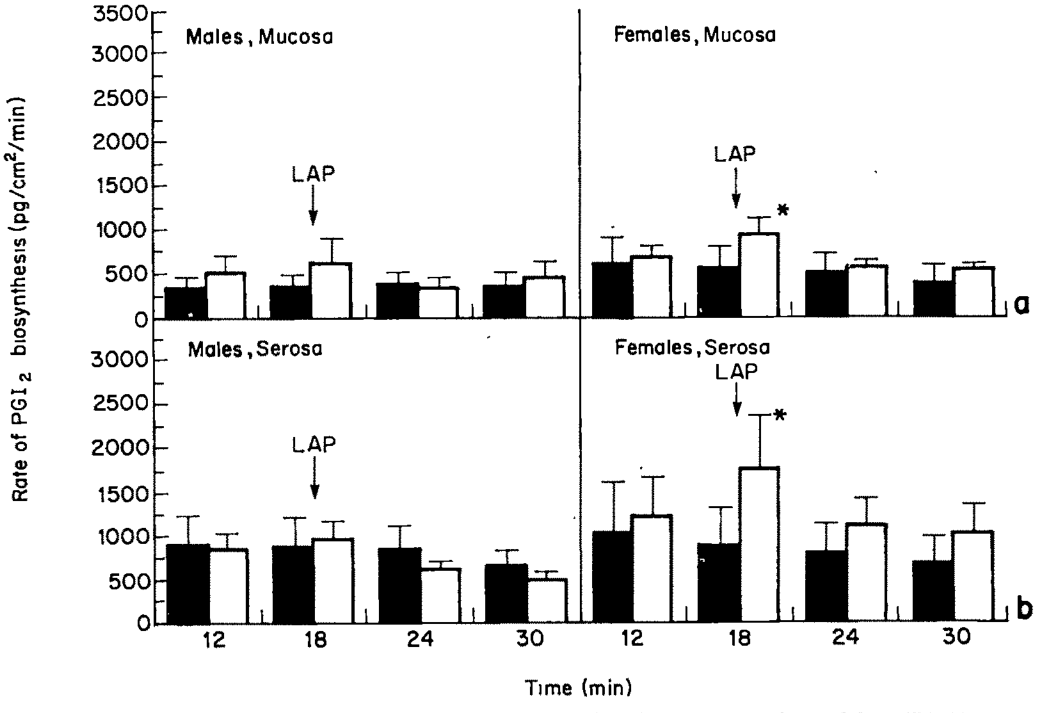

Figure 6 *The effect of LAP on PGI_2 biosynthesis by mucosal (a) and serosal (b) surfaces of the gallbladder from seven male and seven female animals.* ■, *control studies,* □, *LAP studies Data at 12 min represent the average data from the first two 6-min basal periods.* *$P < 0.005$

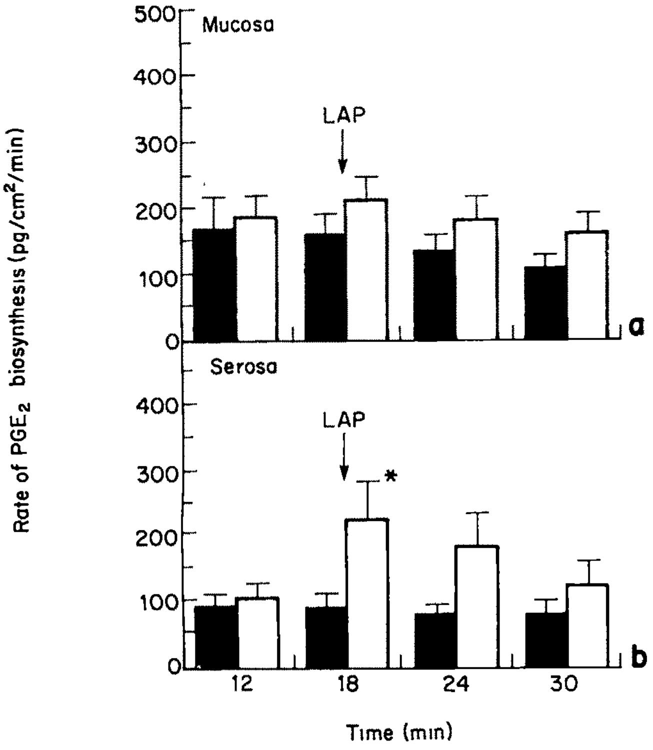

Figure 7 *The effect of LAP on PGE_2 biosynthesis by mucosal (a) and serosal (b) surfaces of the gallbladder from 14 dogs (seven males, seven females).* ■, *control studies,* □, *LAP studies Data at 12 min represent the average data from the first two 6-min control periods* $^*P<0{\cdot}005$

gallbladder. This technique is far simpler than Ussing chambers, since it does not utilize continuous oxygenation. It also allows for multiple simultaneous incubations.

Our studies were conducted in dogs (despite the fact that they rarely get gallstones) since a large number of gallbladder segments were utilized. Although mongrels provided the tissue, the differences among animals were very small, allowing for the collection of uniform data. The stage of oestrus was not considered in the female animals, since our prior studies[12] documented that the oestrus cycle did not play a major role in prostaglandin biosynthesis.

Cyclo-oxygenase inhibition is recognized as a standard technique for documentation of the prostanoid characteristics of the immunoreactive products Our study documented the expected dose-response inhibition by indomethacin Inhibition of prostanoid production by indomethacin has been the most consistent common observation in the literature in studies relating to prostaglandin activity and gallbladder function.

The current study tested the effect of arachidonic acid in stimulating prostanoid synthesis. While La Morte and colleagues[13] have suggested that phospholipase is the controlling enzyme in prostaglandin biosynthesis, it is not surprising that cyclo-oxygenase also plays a role in the control of prostanoid synthesis. Pace-Asciak and Wolfe[14] demonstrated that arachidonic acid stimulated the production of PGE_2 and $PGF_{2\alpha}$ by homogenates of the rat gastric mucosa *in vitro* Using tumour cells, we have documented a linear relationship between PGE_2 and $PGF_{2\alpha}$ synthesized and arachidonic acid added to lysates of the tumour cells[15] Hence, using these models, excess arachidonic acid was utilized in the current studies to assess the ability of gallbladder tissue to convert precursor fatty acid to prostacyclin. No attempt was made to determine how far the arachidonate penetrated into the tissue. However, the fact that we demonstrated no transfer of ^3H-arachidonic acid across the gallbladder wall added validity to our model as a useful *in vitro* method for evaluating possible sites of prostanoid production.

The results of our study demonstrate that canine gallbladder tissue responds to arachidonic acid stimulation but that this effect is differential, i.e. PGI_2 synthesis increased but there was no change in the synthesis of PGE. The maximum rates of arachidonate-stimulated PGI_2 synthesis in females were almost double those noted in males. Myers[16] demonstrated an almost 20-fold higher level of PGI_2 and PGE in gallbladders from female as compared with male rabbits (although there was also a fourfold increase in the amounts of $PGF_{2\alpha}$). Our data show a similar trend. In addition, our results in dogs suggest that PGI_2 plays a more important role in the gallbladder than does PGE, since basally six to ten times as much PGI_2 was produced and this prostanoid was stimulated by arachidonic acid augmentation

In initiating this study, we hoped that by determining possible differences in the rates of synthesis of prostanoids in different layers of the gallbladder wall, we might generate useful information as to the predominant site of production of specific prostaglandins (and hence, provide valuable clues as to their function). In this present study, there was no difference between mucosal and serosal production of either PGI_2 or PGE. Kaminski *et al.*[2], studying human cholecystectomy specimens, separated and isolated mucosal cells in tissue culture and compared their activities with those of homogenates of the muscle layer. They found that PGE and prostaglandin F (PGF) were equally distributed in the mucosal and serosal layers but that with increasing severity of inflammation, PGE synthesis increased but PGF levels remained unchanged. Leyssac *et al.*[7] found that serosal application of PGE_1 and PGE_2 inhibited iso-osmotic fluid transport but that there was little effect when prostaglandins were applied to the mucosa

Phospholipase A_2 removes a fatty acid from the 2-position of phosphoglycerides, producing a lysophosphoglyceride The most abundant phosphoglycerides in higher plants and animals are phosphatidylethanolamine and phosphatidylcholine, commonly referred to as cephalin and lecithin, respectively. These two compounds are the major components of animal cell membranes from which the precursors of the cyclo-oxygenase pathway are derived. In contrast, arachidonic acid is derived directly from linoleic acid, an essential fatty acid

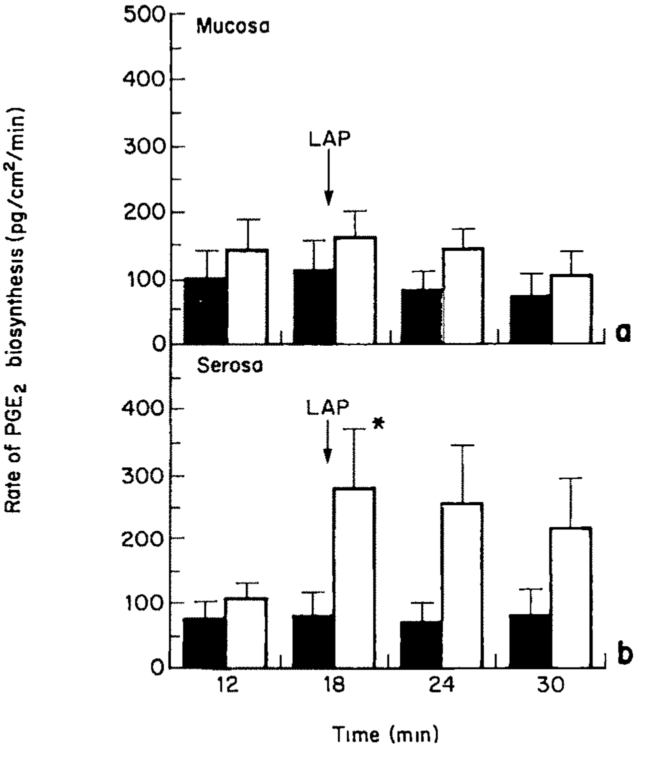

Figure 8 *The effect of LAP on PGE_2 biosynthesis by mucosal (a) and serosal (b) surfaces of the gallbladder from seven female animals* ■, *control studies,* □, *LAP studies. Data at 12 min represent the average data from the first two 6-min basal periods* $^*P<0{\cdot}005$

which cannot be synthesized by mammals and is obtained only from plant sources.

Although in most tissues, prostaglandin synthesis is controlled by phospholipase A_2, it is unclear whether this system operates in the gallbladder. In 1979, Tagesson and co-workers reported the presence of a calcium-dependent phospholipase A_2 system in gallbladder tissue[17]. However, in 1981, Rutledge and co-workers were unable to identify this enzyme system in gallbladder homogenates[18].

Since, in this study, exogenous LAP resulted in increased PGI_2 and PGE_2 production by full-thickness segments of gallbladder tissue, our results suggest that phospholipase A_2 probably does play a major role in biliary eicosanoid biosynthesis. It is important to point out that arachidonic acid pulsing (25 mM) did not significantly stimulate PGE_2 biosynthesis whereas addition of phosphatidylcholine did. This observation is consistent with an important role for phospholipase but not for cyclo-oxygenase. This, and the multiple other differences noted in the effects of arachidonate and LAP, suggests that the two agents work via different enzymatic systems.

The role of phospholipids in biliary tract inflammation and stone formation is still unclear. Gallbladder bile concentrations of lysophosphatidylcholine (lysolecithin) are elevated in patients with acute cholecystitis[19,20]. Lysolecithin has been shown experimentally to induce acute cholecystitis in rabbits[21,22]. In this species, lysolecithin has been shown to induce dose-related increases in enzyme release and vascular permeability. The feline studies of Neiderheiser and colleagues[23] demonstrated that lysophosphatidylcholine induced histological changes of acute cholecystitis and caused basal fluid secretion (rather than absorption) in the gallbladder. The potent effects were shown to be eicosanoid-mediated, in that they were significantly inhibited by indomethacin, a potent inhibitor of endogenous prostaglandin biosynthesis. Finally, Thornell and colleagues[24] documented that in feline experimental cholecystitis, lysophosphatidylcholine induced an exaggerated rate of biosynthesis of PGE_2.

We conclude that this new *in vitro* technique provides a useful model for simultaneous, independent incubation of both surfaces of the gallbladder. The tissue in the chamber is capable of local synthesis of PGI_2 and PGE, and indomethacin inhibits in a predictable manner. We propose the chamber as a useful model for further elucidation of the role of prostanoids and phospholipids in an attempt to decipher the sequence of events in the pathogenesis of gallbladder disease.

Acknowledgement

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Tissue plasminogen activator in peripheral arterial thrombolysis

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Thirty acute peripheral arterial thromboses in 28 patients were treated with local low-dose intra-arterial recombinant tissue plasminogen activator (t-PA). All patients received 0·5 mg h^{-1} *t-PA and 15 also received 250 units h*$^{-1}$ *of intra-arterial heparin. Overall limb salvage at 30 days was 83 per cent (25 out of 30 limbs). Mean(s.d.) ankle/brachial index was increased by 0·53(0·26) and there was no significant difference between the group receiving t-PA alone and that receiving t-PA and heparin. No strokes or major haemorrhages occurred but there were four (13 per cent) minor haematomas associated with the catheter entry site. There were four (13 per cent) deaths from myocardial infarction occurring between 5 and 21 days after treatment. Rethrombosis occurred in four cases (13 per cent). In two patients following t-PA alone, rethrombosis occurred after 2 and 11 days. Limb salvage was achieved with a successful repeat thrombolysis and a femoropopliteal graft respectively. Rethrombosis after t-PA and heparin occurred after 30 days in two patients due to poor run-off and extensive proximal atheromatous disease respectively. t-PA is a safe, effective thrombolytic agent when given as a low-dose intra-arterial infusion. The addition of low-dose heparin does not produce any significant benefit.*

Keywords: Tissue plasminogen activator, thrombolysis, limb salvage

There is a resurgence of interest in the technique of local thrombolysis for acute and subacute peripheral arterial thromboses. Most experience is with streptokinase[1–5], but recently recombinant tissue plasminogen activator (t-PA) has become available with the promise of more rapid and yet more specific thrombolysis[6–10]. In coronary arteries, t-PA has been shown to offer a more rapid lysis than conventional treatment with streptokinase[11–14]. However, experience with t-PA for peripheral arterial thrombolysis is still comparatively recent[6–10]. In particular, centres using t-PA have progressively reduced their doses, albeit within different dose regimes. The overall conclusion one may draw from these studies is that t-PA is a potent thrombolytic agent and that the dose may be reduced further without loss of lysis. In this centre the lowest dose currently reported is used with a success comparable with that in centres using much higher doses

Patients and methods

Patients with a clinically obvious embolus <2 days old underwent balloon embolectomy and patients with severe arterial ischaemia (loss of sensation and/or motor loss) were not included in the study as the time required to achieve thrombolysis would have exceeded the viability time of the affected limb (*Figure 1*) All other patients with a history of a sudden deterioration in, or onset of, lower limb ischaemia of up to 30 days duration were considered eligible for thrombolysis after informed consent had been obtained

At the time of diagnostic femoral arteriography, a 4 Fr or 5 Fr intra-arterial catheter was inserted for 1–2 cm into the thrombus. For lesions >25 cm the catheter was inserted to within 10–15 cm of the distal extent of the thrombus As lysis proceeded the catheter was gradually withdrawn. For iliac or flush superficial femoral lesions, the catheter was inserted via the contralateral femoral artery, and for femoral and popliteal lesions it was inserted through the ipsilateral femoral artery

Thirty acute peripheral arterial thromboses were treated in 28 patients All patients received 0 5 mg h^{-1} t-PA (Boehringer Ingelheim, Bracknell, Berkshire) intra-arterially. In addition, 15 of these patients also received 250 units h^{-1} of intra-arterial heparin. Patients were nursed in a side ward with hourly records made of blood pressure, pulse and temperature. Fibrinolytic parameters were assessed after 4 h, then at 12-h intervals throughout therapy. A single injection arteriogram using iopamidol (Niopam® 300, E Merck Ltd , Alton, UK) was performed at these intervals using mobile X-ray equipment on the ward Infusions were continued until full lysis was achieved as confirmed by clinical and angiographic reperfusion Residual stenoses were dilated before removal of the catheter

After successful thrombolysis/angioplasty, the patients were anticoagulated with heparin for 5 days, with warfarin commencing on the third day. Heparin was only started after assessing the extent of systemic fibrinolysis. Any grossly deranged values such as thrombin clotting time in excess of 60 s resulted in a deferred start until this had returned to less than 60 s

Thrombin clotting time (TCT), international normalized ratio (INR), activated partial thromboplastin time (APTT), plasminogen and alpha-2-antiplasmin were estimated on venous blood samples collected in one-tenth their volume of 3·8 per cent trisodium citrate dihydrate Platelet-poor plasma was obtained by centrifuging the citrated samples at 1500 g for 10 min This was either tested immediately or frozen to −70°C for analysis later in batches. Alpha-2-antiplasmin and plasminogen assays were performed using a synthetic chromogenic substrate (S2251, Kabi-Vitrum, Stockholm, Sweden)[9,10]. Fibrinogen was measured on venous samples transferred into one-tenth their volume of 3·8 per cent trisodium citrate dihydrate and 10 per cent aprotinin (Trasylol, Bayer UK Ltd) and stored as above Samples were analysed in batches by the method of Clauss[15]. Euglobulin clot lysis times were estimated by the method of Buckell[16]. Fibrin/fibrinogen degradation product (FDP) assays were carried out on 2 ml venous kit (Dade Diagnostics) Full blood counts were performed on sequestrene samples using a Coulter S plus IV counter (Coulter Electronics, Itialeah, France)

Absolute contraindications to treatment with thrombolytic agents were active or recent bleeding in the last month, blood dyscrasias, active peptic ulceration, stroke within the last 2 months, or recent trauma or major surgery[17].

Results are expressed as mean(s d.) values Statistical analysis was performed using the Mann–Whitney *U* test or χ^2 analysis

Results

Overall limb salvage at 30 days was 83 per cent (25 out of 30 limbs; *Table 1*). Despite successful lysis of an acute iliac thrombosis, amputation was still required in one patient due to established gangrene. Mean(s.d.) ankle/brachial index was increased by 0·53(0·26) There was no significant difference in

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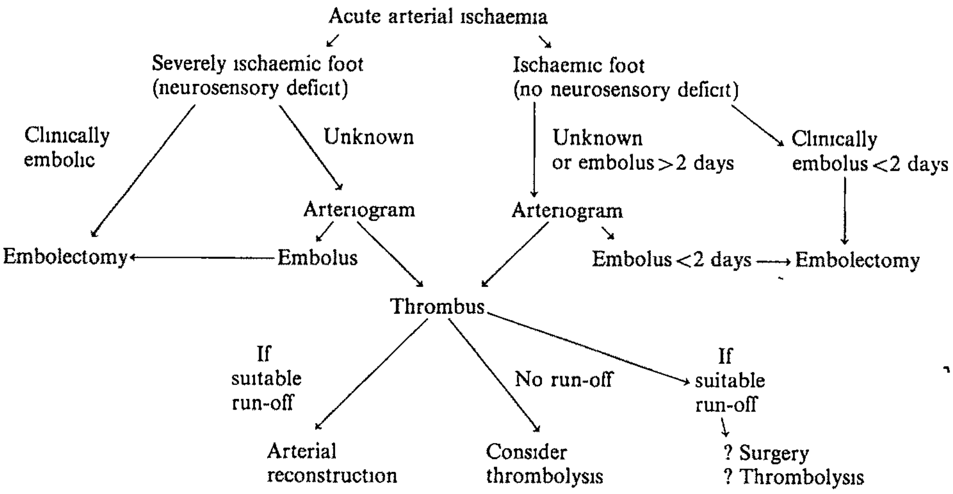

Figure 1 *Treatment protocol*

Table 1 *Patient details*

	t-PA group	t-PA + heparin group	Total
No. of limbs	15	15	30
Age (years)	75(12)	70(11)	72(12)
Duration of history (days)	16(10)	17(10)	17(10)
Length of occlusion	18(14)	20(15)	19(14)
Ankle/brachial index increase	0·43(0·24)	0·58(0·29)	0·53(0·26)
Duration of infusion (h)	26(13)	32(18)	29(16)
No. of limbs salvaged at 30 days	13(87%)	12(80%)	25(83%)

t-PA, tissue plasminogen activator. Values are expressed as mean(s.d.)

these parameters between the group receiving and the group not receiving heparin; however there was a trend which did not reach statistical significance towards a longer mean(s.d.) duration of therapy in the heparin group, 32(18) h compared with 26(13) h. Sixteen limbs (53 per cent) required angioplasty for residual stenoses. All lesions were in native vessels. There were no prosthetic or saphenous vein graft thromboses and no thrombosed popliteal aneurysms. *Table 2* shows the distribution of the lesions treated.

No strokes or major haemorrhages occurred. Minor haematomas associated with the catheter entry site occurred in four patients (13 per cent) and one patient experienced extravasation of contrast into the calf. There were four deaths (13 per cent) from myocardial infarction occurring between 5 and 21 days after treatment. Rethrombosis occurred in four cases (13 per cent). In two patients given t-PA alone, these occurred after 2 and 11 days. Limb salvage was achieved with a successful repeated, thrombolysis in one case and a femoropopliteal graft in the other. Rethrombosis following concurrent therapy with low-dose heparin occurred in two patients after 30 days due to poor run-off in one and extensive proximal atheromatous disease in the other. Eight (27 per cent) occlusions were >25 cm. For t-PA alone the mean(s.d.) length of occlusion was 18(14) cm, and for t-PA with concurrent heparin 20(15) cm. This difference was not statistically significant.

No transfusions were required and no periods of hypotension occurred. Haemoglobin levels fell by a mean(s.d.) of 0·84(0·83) g dl^{-1} overall; however there was a significantly greater fall (albeit small) with t-PA alone than with concurrent heparin (*Table 3*). Plasminogen and alpha-2-antiplasmin levels were significantly lower with t-PA alone than with concurrent heparin (*Table 3*).

Table 2 *Distribution of lesions*

Site	No. of lesions
Common/external iliac	7 (23)
Superficial femoral/popliteal	17 (57)
Popliteal/tibial/peroneal	6 (20)

Values in parentheses are percentages of total

Table 3 *Systemic effects of t-PA and t-PA + heparin*

	t-PA group	t-PA + heparin group	Significance
Reduction in haemoglobin	1·2(0·9)	0·5(0·7)	$P<0·01$
Maximal reduction in plasminogen (%)	58·5(29·6)	83·3(8·8)	$P<0·01$
Maximal reduction in fibrinogen (%)	66·1(23·2)	72·2(19·6)	Not significant
Maximal reduction in alpha-2-antiplasmin (%)	40·4(17·6)	64·1(18·3)	$P<0·01$

t-PA, tissue plasminogen activator. Values are expressed as mean(s.d.)
All statistics performed using Mann–Whitney *U* test

Discussion

Local low-dose peripheral arterial thrombolytic therapy can offer several advantages over conventional surgical intervention. The risk of a general anaesthetic is removed. It allows improved definition of occult underlying disease and it allows appropriate intervention usually in the form of percutaneous transluminal angioplasty. It can also lyse inaccessible thrombi or emboli in small peripheral or collateral vessels[18–20]. Thrombolytic therapy does not prejudice subsequent surgery but initial surgery does prejudice subsequent thrombolytic therapy. Hence, if the limb can survive for approximately 24 h, thrombolysis can be considered. Thrombolysis may obviate the need for subsequent surgery and, even if it fails, surgery can still proceed.

Emboli of <2 days duration were excluded in the present study. However, as further experience is gained with this technique, particularly using t-PA, such emboli may come to be treated in the future. A randomized controlled study is required comparing thrombolysis with conventional balloon embolectomy in such patients. Patients with neurosensory deficit were also excluded because the time required to achieve thrombolysis was deemed to exceed the likely duration of tissue viability of the compromised limb.

Despite a local low-dose administration, the use of streptokinase is associated with a profound systemic effect[1,21]. This is because it activates the fibrinolytic system by converting both circulating and fibrin-bound plasminogen into plasmin, which then digests fibrin. Initial experience with t-PA, however, has shown it to be a relatively fibrin-specific agent which is activated by fibrin-bound plasminogen, and which has a potential for greater efficacy and safety than streptokinase[10,14,21,22] or urokinase[23]. Furthermore, the development of anti-streptokinase antibodies precludes any repeat therapy with streptokinase.

The addition of low-dose heparin to t-PA has not produced any significant benefit in the present study, and may have contributed to a tendency to a longer duration of therapy. This may be explained by a protection of plasminogen, alpha-2-antiplasmin and haemoglobin levels, suggesting that heparin, by an unknown mechanism, may inhibit the fibrinolytic capacity of t-PA, so increasing the lysis time and reducing the bleeding tendency It is known that t-PA has important platelet anti-aggregatory effects and the addition of heparin, which can promote platelet aggregation[24,25], may be counteracting this clinically useful effect

The overall limb salvage rate was 83 per cent. This compares favourably with previous reports of limb salvage rates of 59–69 per cent using streptokinase[8,13] and 35 per cent using acylated plasminogen activator complex[26]. In addition t-PA has the advantages of a significantly reduced systemic effect[10], a tendency to a shorter duration of infusion, and is associated with fewer haemorrhagic complications[7,21]. Similarly, in coronary thrombolysis, compared with streptokinase therapy t-PA appears to offer a more rapid and effective thrombolytic action[11–14]. Although the risk of anaphylactic reaction from streptokinase in small, it may be severe[27].

Graor and Risius[28] reported a marked reduction of alpha-2-antiplasmin to zero with both doses of t-PA used (0·05 and 0·1 mg kg^{-1} h^{-1}). Significantly less inhibition was seen at 2 h than at 4 or 6 h of infusion with both doses. Similarly fibrinogen levels were reduced to 35 per cent (0·1 mg kg^{-1} h^{-1}) or 40 per cent (0·05 mg kg^{-1} h^{-1}) of original levels. Plasminogen levels were reduced by 75 per cent with 0·1 mg kg^{-1} h^{-1} and by 50 per cent with 0·05 mg kg^{-1} h^{-1}. All of these parameters were considerably reduced compared with our data. Direct comparison between the two studies is difficult due to the wide differences in patient age (mean 58 years), age of occlusion (mean 7·5 days), and the proportion of native vessels treated compared with thrombosed grafts (50 per cent). The equivalent dose for a 70 kg man would be 3·5–7 mg h^{-1} and the profound systemic effects may be due to the comparatively high doses used It is notable that the same group have subsequently shown no difference between the two doses and are now using the lower dose[7]. Similarly, in the study of Verstraete *et al* [9], efficacy was retained by reducing from 10 mg h^{-1} to 5 mg h^{-1} and then to 3 mg h^{-1}. However, bleeding complications were not reduced. In this particular study acute arterial thromboses were excluded and the clinical necessity for high-dose, short duration therapy is dubious Furthermore, the amount of t-PA used at 10 mg h^{-1} was 27 mg, at 5 mg h^{-1} it was 39 mg and at 3 mg h^{-1} it was 42 mg, which must be compared with a mean dose of 15 mg in the present study in which acute arterial thromboses were also included. Verstraete *et al.* also documented three (5·5 per cent) major haemorrhages and one (1·8 per cent) cerebrovascular accident which occurred 48 h after therapy whilst on heparin. Although it is true that longer infusions generate more profound systemic lytic effects, this is dose-dependent.

The present study shows that a much lower dose of t-PA gives acceptable lysis and achieves a substantial increase in ankle/brachial index with a much reduced systemic effects These results confirm t-PA to be a relatively fibrin-specific thrombolytic agent which can achieve excellent limb salvage in patients with acute arterial thromboses

Acknowledgements

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Common femoral artery volume flow in peripheral vascular disease

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Common femoral artery volume flow was measured at rest and during postocclusive reactive hyperaemia in 80 normal subjects and 67 patients with radiological evidence of occlusive peripheral vascular disease. At rest, mean(s.d.) common femoral artery volume flow in normal subjects (344(135) ml/min) and all patients with peripheral vascular disease (401(168) ml/min) was not significantly different. During postocclusive reactive hyperaemia, mean(s.d.) peak flow was significantly higher in normal subjects (1951(438) ml/min) than in patients with peripheral vascular disease (996(457) ml/min) ($P<0{\cdot}01$*). Common femoral artery volume flow in patients with critical ischaemia and intermittent claudication did not differ at rest but mean(s.d.) peak flow in patients with critical ischaemia (697(276) ml/min) was significantly lower than in claudicants (1131(447) ml/min) (*$P<0{\cdot}01$*). Mean(s.d.) resting common femoral artery volume flow in limbs with femoropopliteal disease (457(185) ml/min) was significantly greater than that in limbs with occlusion of the aortoiliac segment (308(130) ml/min) (*$P<0{\cdot}01$*). However, this difference did not persist during postocclusive reactive hyperaemia. A hyperaemic index, calculated from the hyperaemic responses to below knee and whole limb ischaemia, was used to quantify segmental perfusion during postocclusive reactive hyperaemia. The mean(s.d.) value in normal subjects, 46(9) per cent, and in those with aortoiliac disease, 52(12) per cent, indicated approximately equal perfusion of the above and below knee limb segments. In those with femoropopliteal disease the mean(s.d.) hyperaemic index was 17(13) per cent, revealing relative hypoperfusion of the below knee segment.*

Keywords: Common femoral artery, volume flow, hyperanaemic index

Since the advent of modern peripheral vascular surgery there have been extensive haemodynamic studies of atherosclerotic disease of the lower limb. The clinically important concepts of critical ischaemia and the 'surgically important' arterial segment remain the subject of much research and discussion.

Arteriography is the widely used 'gold standard' investigation in peripheral vascular disease but the information obtained is purely morphological. In contrast, blood volume flow is currently regarded as the best index of tissue perfusion[1] Because of the development of duplex ultrasound systems[2] it has become possible to measure blood volume flow non-invasively.

This is a report of the results of volume flow measurement in the common femoral artery. The applicability of this haemodynamic measurement in the assessment of patients with peripheral vascular disease is discussed.

Patients and methods

Patients

Measurements were carried out on normal, healthy, volunteers with no clinical evidence of atherosclerosis and on patients with radiological evidence of occlusive peripheral vascular disease A total of 109 limbs was studied in 80 normal volunteers, comprising 38 men and 42 women, with a mean age of 40 years (range 21–63 years).

A total of 77 limbs was studied in 67 patients with occlusive peripheral vascular disease, comprising 52 men and 15 women, with a mean age of 62 years (range 38–86 years). These patients were divided into subgroups according to the clinical and radiological features of the disease (*Table 1*)

Methods

Apparatus and technique Volume flow was measured in the common femoral artery using a real-time audio spectrum analyser (Vasoscan) interfaced to a duplex scanner (ATL Mk600 PV Duplex Ultrasound System) The duplex scanner initially visualized the common femoral artery and imaged along its longitudinal axis The real-time display was then 'frozen' and the vessel diameter and angle of insonation measured with caliper and cursor respectively After positioning the sample volume to cover the vessel lumen, the Doppler-mode was selected and the phase quadrature Doppler-shift signals were fed into the spectrum analyser This instrument was programmed to derive the time averaged mean Doppler-shift frequency which was stored in the computer memory. Values for the angle of insonation and vessel diameter were keyed in and the corresponding volume flow was calculated and displayed on the screen. The volume, Q, is given by·

$$Q=\frac{\pi D^2}{4}\bar{V}$$

Table 1 *Subgroups of patients with peripheral vascular disease*

Subgroup	No of limbs
Clinical	
Intermittent claudication	54 (70)
Critical ischaemia (rest pain, ischaemic ulceration, gangrene)	23 (30)
Radiological	
Aortoiliac disease	28 (36)
Femoropopliteal disease	37 (48)
Combined segment disease	12 (16)

Values in parentheses are percentages

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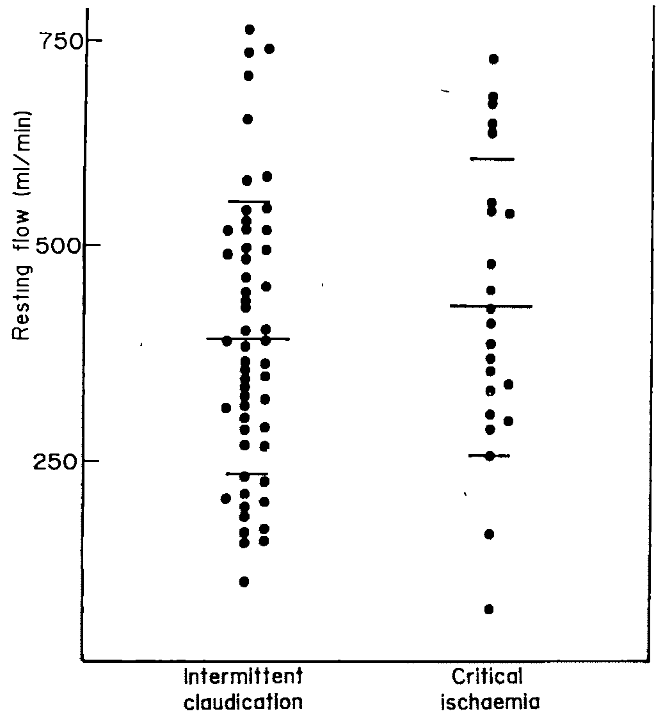

Figure 1 *Resting common femoral artery volume flow, effect of the clinical stage of peripheral vascular disease*

where D is the vessel diameter and $\bar{V}$ the time average mean velocity across the vessel cross-section.

Conditions of measurement. Studies were performed in a quiet, temperature controlled, laboratory situated at the periphery of the hospital. The common femoral artery was investigated under resting conditions and after the induction of limb ischaemia

At rest measurements were obtained after a 25 min period of inactivity in the supine examination position[3]

Limb ischaemia was produced by placing a conventional sphygmomanometer cuff around the limb and inflating it to above systolic blood pressure for 2 min. When the circulation was restored, volume flow in the common femoral artery was calculated sequentially at intervals of 3 s until the reactive hyperaemia response waned[4]. The value of peak flow was then recorded

Peak flow in the common femoral artery was determined after ischaemia of the 'whole limb' and 'below knee' segments using arterial occlusion cuffs placed high on the thigh and immediately below the knee respectively A hyperaemic index (per cent) was calculated from the formula·

$$HI=\left(\frac{PFBK-RF}{PFWL-RF}\right)\times 100$$

where HI = hyperaemic index, PFBK = peak flow after ischaemia of the below knee segment, PFWL = peak flow after ischaemia of the whole limb segment, and RF = resting common femoral artery blood flow

Statistical analysis The numbers (n) of limbs studied are indicated The values quoted refer to the mean and standard deviation in parentheses. Statistical analysis of the data was performed using the Mann–Whitney U test for non-parametric data

Results

Common femoral artery volume flow at rest

In normal subjects ($n=109$ limbs) resting common femoral artery volume flow was 344(135) ml/min (range 109–714 ml/min). There was no relationship between blood flow and either the age or sex In patients with occlusive peripheral vascular disease ($n=77$ limbs) resting common femoral artery volume flow was 401(168) ml/min (range 72–760 ml/min). The difference in resting blood flow between normal subjects and arteriopaths was not statistically significant.

There was no significant difference between resting common femoral artery blood flow in limbs affected by intermittent claudication (390(166) ml/min, $n=54$) and critical ischaemia (429(177) ml/min, $n=23$) (*Figure 1*). However, blood flow in critically ischaemic limbs was 25 per cent higher than in normal subjects. This difference was statistically significant ($P<0\cdot05$)

Blood flow in limbs with isolated aortoiliac disease (308(130) ml/min, $n=28$) was significantly lower than in limbs with isolated femoropopliteal disease (457(185) ml/min, $n=37$; $P<0\cdot01$) and limbs with combined segment disease (447(183) ml/min, $n=12$, $P<0\cdot05$). There was no statistical difference between blood flow in limbs with isolated femoropopliteal disease and combined segment disease (*Figure 2*).

Common femoral artery volume flow during hyperaemia

In normal subjects ($n=32$) whole limb ischaemia produced a marked hyperaemic response. Common femoral artery volume flow at rest before ischaemia (358(125) ml/min) rose after circulatory release to a peak flow of 1951(438) ml/min, approximately five and a half times greater than the resting level. The same circulatory stress in patients with peripheral vascular disease ($n=44$) produced a smaller increase in blood flow, from 365(147) ml/min at rest to a peak flow of 996(457) ml/min. Peak flow in normal subjects was approximately twice that in patients with peripheral vascular disease, a highly significant difference ($P<0\cdot01$). However, 27 per cent of peak flow values in diseased limbs were within the normal range (*Figure 3*).

Peak flow after whole limb ischaemia in patients with intermittent claudication (1131(447) ml/min, $n=32$) was significantly higher than in patients with critical ischaemia (697(276) ml/min, $n=12$; $P<0\cdot01$). Although peak flow values in limbs with critical ischaemia were invariably below the normal range, they overlapped considerably with the range of values in limbs with intermittent claudication (*Figure 4*).

Peak flow after whole limb ischaemia in limbs with combined segment disease (668(258) ml/min, $n=8$) was significantly lower than in limbs with aortoiliac disease (1081(469) ml/min, $n=17$, $P<0\cdot05$) and limbs with femoropopliteal disease (1048(475) ml/min, $n=19$; $P<0\cdot05$) (*Figure 5*). There was no statistical difference between peak flow in limbs with isolated aortoiliac and femoropopliteal disease.

In normal subjects ($n=11$) peak flow in the common femoral artery after selective ischaemia of the below knee segment was 1038(209) ml/min. This value was approximately half the

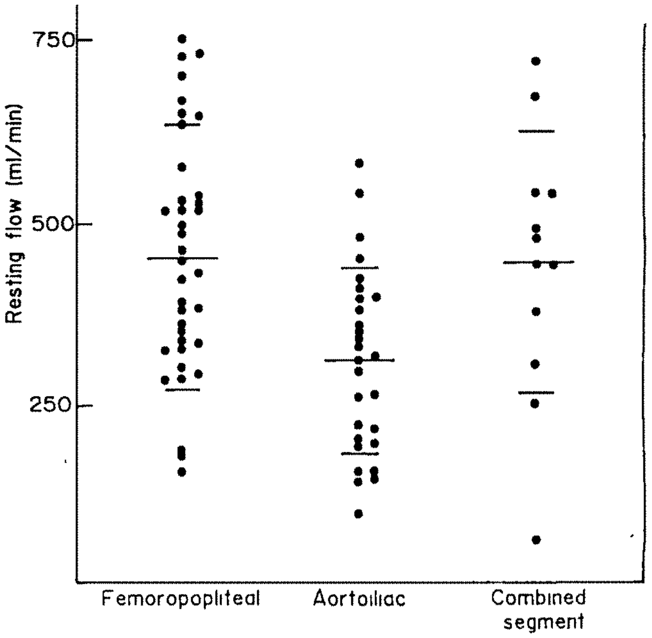

Figure 2 *Resting common femoral artery volume flow, effect of the radiological site of arterial occlusion*

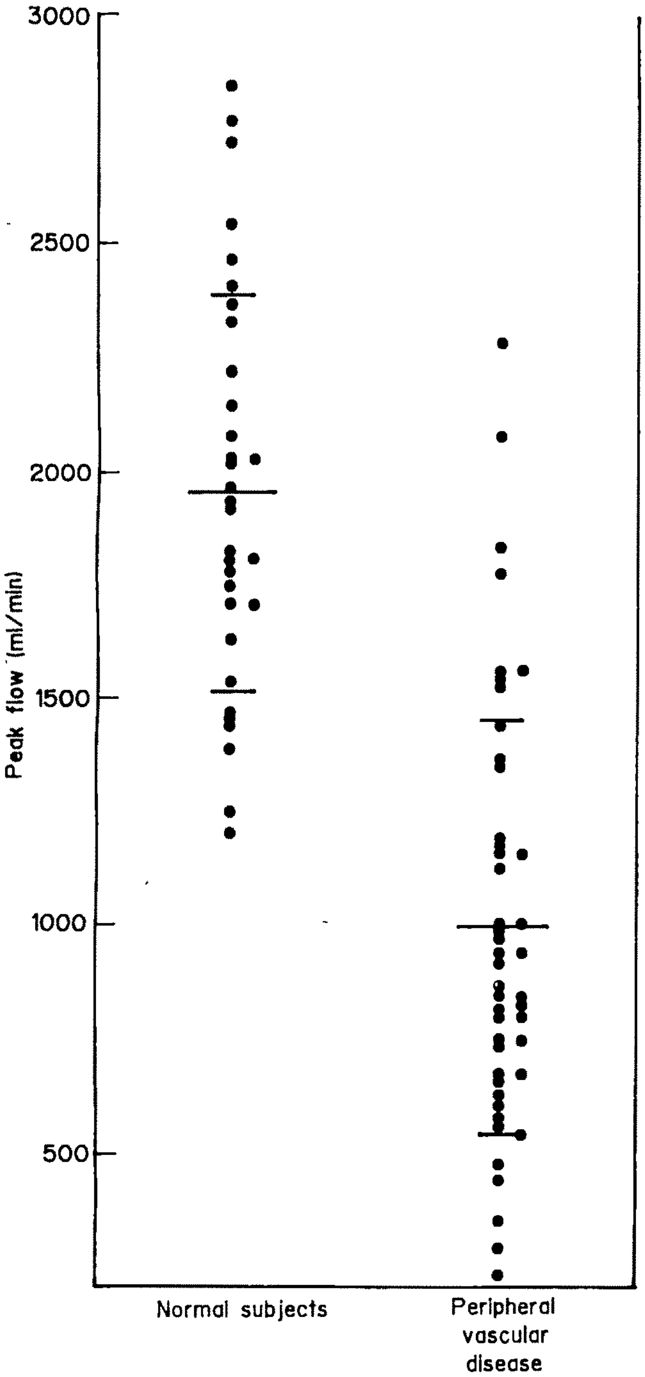

Figure 3 *A comparison between the range of peak flow in normal subjects and patients with peripheral vascular disease*

corresponding result after whole limb ischaemia (1918(463) ml/min). The average value of the hyperaemic index in these subjects was 46(9) per cent (range 36–65 per cent) In patients with isolated aortoiliac disease ($n = 8$) the hyperaemic index was 52(12) per cent (range 35–74 per cent) which was similar to that observed in normal subjects. The hyperaemic index in patients with isolated femoropopliteal disease ($n = 13$) was 17(13) per cent (range 0–34 per cent), significantly lower than in patients with aortoiliac disease ($P < 0.01$) and with a clear separation of values between the groups (*Figure 6*).

Discussion

There is no generally agreed value for resting common femoral artery volume flow in normal subjects. Previous studies have revealed considerable variability in blood flow and also divergent results. Even Fitzgerald and O'Shaughnessy[5], who used a similar Doppler-shift technique, reported a different value (266(111) ml/min) approximately 30 per cent lower than that obtained in the present study (334(135) ml/min). The wide range of flow rates obtained from individual vessels is probably largely a result of physiological fluctuation Laboratory investigations, using test rigs, have shown that duplex ultrasound systems provide an accurate measure of volume flow[6–9], however, when operator error is fixed by repeated measurements with a scan head clamped in position, a large variability in flow rate still exists[4] This variability (approximately 75 per cent of the total intersubject variability in volume flow[4]) is probably due to physiological changes, although this conclusion is difficult to substantiate by simultaneous direct estimation of cardiac output, peripheral resistance and limb vascular volume.

At rest there was no difference in common femoral artery volume flow between normal subjects and patients with peripheral vascular disease. Although this observation has been widely documented in reports of calf blood flow measurement using plethysmography[10–13], the results of resting common femoral artery volume flow measurement by indicator dilution techniques are less consistent, with some authors finding lower values in diseased limbs[14,15]. Both of these earlier types of study were performed mainly on patients with intermittent claudication. Also included in the present study were a number of patients with critical ischaemia, in whom blood flow at rest was significantly higher than in normal subjects Although these patients with critically ischaemic limbs were frequently found

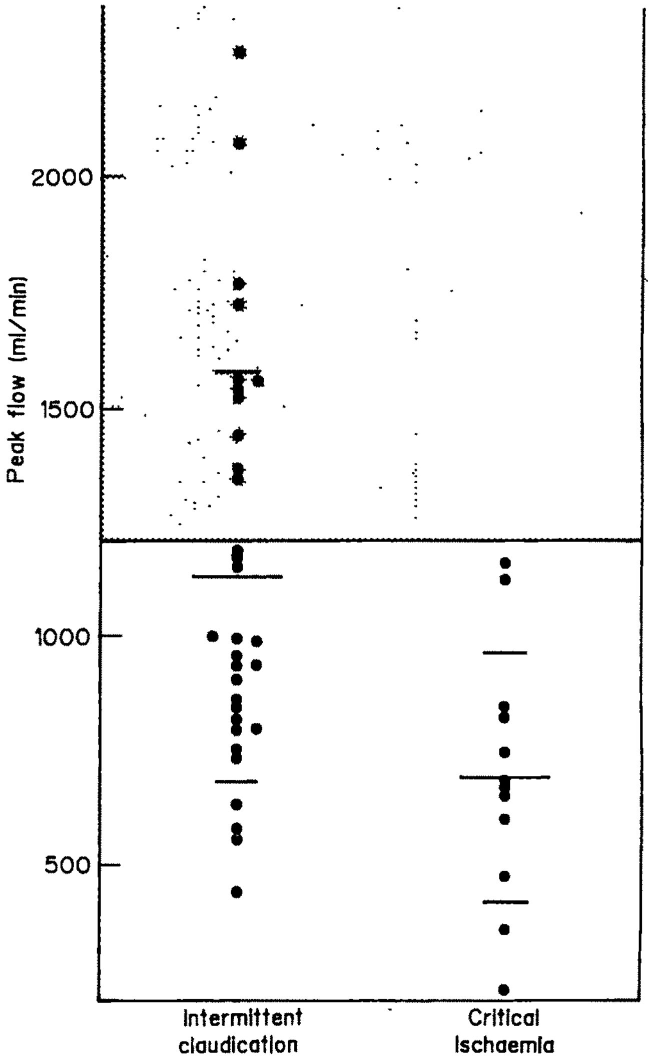

Figure 4 *Peak flow in the common femoral artery effect of the clinical stage of peripheral vascular disease. Shaded area represents normal range*

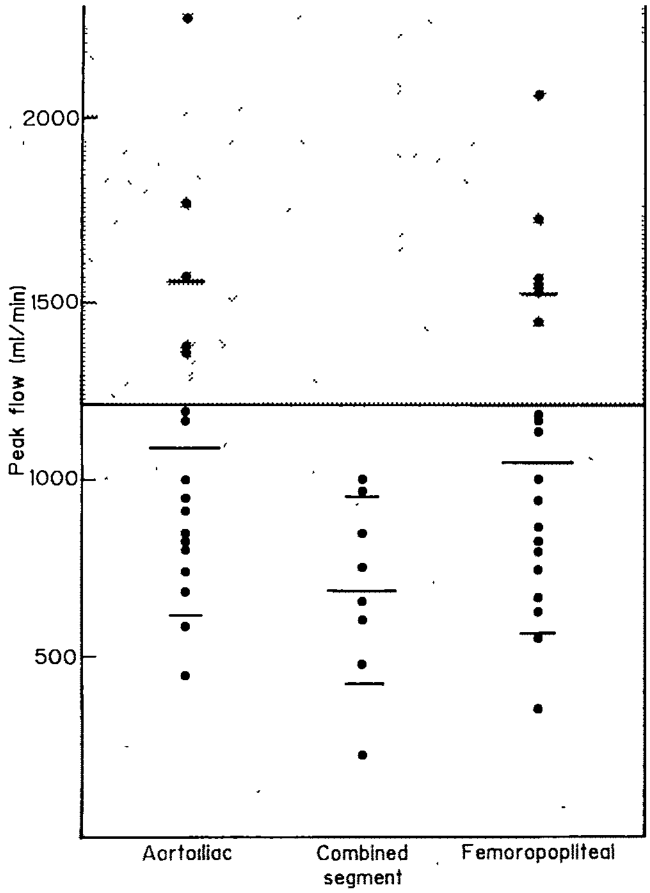

Figure 5 *Peak flow in the common femoral artery: effect of the radiological site of arterial occlusion. Shaded area represents normal range*

to have Doppler-shift spectra with features of peripheral vasodilation, flow in this subgroup was not statistically different from that in patients with intermittent claudication. This result is contrary to the original observations, by Schraibman and Ledingham[16] and McEwan and Ledingham[17], suggesting that foot blood flow is higher in critically ischaemic patients than in claudicants. The discrepancy probably arises because blood flow measurements at the level of the common femoral artery are made too proximally to detect all but the most marked effects of vasodilation occurring adjacent to areas of distal ischaemia.

Resting common femoral artery volume flow in limbs with femoropopliteal and combined segment disease were both significantly higher than in limbs with isolated aortoiliac disease. A possible explanation is that the profunda femoris artery offers a lower resistance to blood flow than the collaterals around an aortoiliac occlusion[18]. In cases of combined segment disease a patent profunda femoris artery may even compensate for the effect of a raised proximal resistance.

Peak flow in normal subjects after 2 min ischaemia of the whole limb was equivalent to femoral blood flow during mild exercise[15,19–21]. The corresponding value in arteriopaths was significantly lower, a finding well documented in plethysmographic studies of calf blood flow[10,13,22–27]. Whereas in the present study peak flow for normal subjects was twice the value for patients with peripheral vascular disease, in calf blood flow studies the average peak flow in normal limbs was between 2·5 and 6 times greater than in diseased limbs[12,13,27,28], implying better discrimination between the two groups.

Because plethysmographic studies were normally performed after 5 min limb ischaemia it is likely that a greater degree of circulatory stress would have resulted in a wider difference between common femoral artery blood flow in normal and diseased limbs. Indeed indicator and thermal dilution studies of common femoral artery blood flow during exercise have revealed an overlap of values in normal and diseased limbs at lower work intensities, but a complete separation of values at high work intensities[22–29]. In the present study the duration of ischaemia was limited to 2 min by an inability to calibrate the apparatus at higher flow rates which were often associated with poor quality Doppler-shift spectra

Peak flow in patients with intermittent claudication was significantly higher than in patients with critical ischaemia. However, the overlap of values suggests that peak flow in the common femoral artery after 2 min whole limb ischaemia does not provide sufficient discrimination for use as a haemodynamic criterion of critical ischaemia[30]. Similarly, determination of peak flow after whole limb ischaemia did not distinguish between limbs with isolated occlusions in the aortoiliac and femoropopliteal segments respectively, despite the difference in resting common femoral artery volume flow between the two groups. Other workers have found peak flow after ischaemia in limbs with femoropopliteal disease to be higher[24] and lower[13] than in limbs with occlusion of the iliac arteries. The results of the present study support the findings of Myers[11] who also reported that peak flow was not related to the site of an isolated occlusion.

A hyperaemic index was devised to quantify the effect of postocclusive reactive hyperaemia on sequential perfusion of the lower limb. In normal subjects the average hyperaemic index was 46 per cent, indicating that during postocclusive reactive hyperaemia perfusion of the above and below knee segments was approximately equal. All values in limbs with isolated aortoiliac disease were within the normal range implying a similar pattern of limb perfusion. The hyperaemic

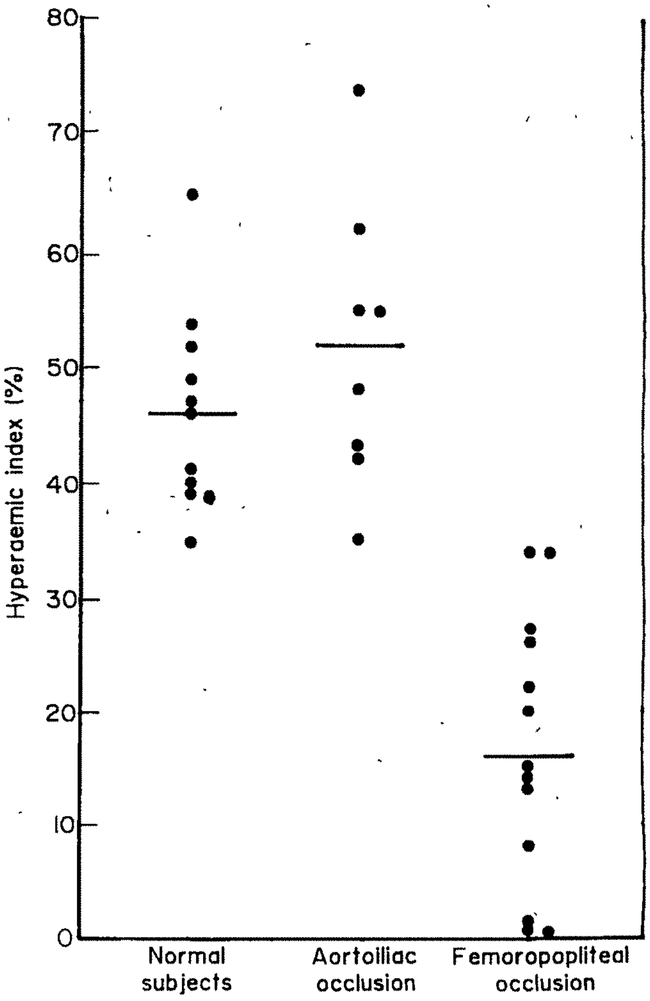

Figure 6 *The effect of the radiological level of an isolated arterial occlusion on the hyperaemic index*

index in limbs with isolated femoropopliteal disease was significantly lower, to the extent that there was no overlap between values in the radiological subgroups. This suggests a relative hypoperfusion of the below knee segment during hyperaemia in limbs with femoropopliteal disease.

This aspect of the hyperaemic response has been largely overlooked in previous limb blood flow studies and also in investigations of limb ischaemia using Doppler-shift waveform analysis Indeed many parameters used to assess the level of arterial occlusion, such as pulsatility index, have been criticized on the grounds that values are influenced to an unknown extent by the degree of distal vascular resistance. In our experience, segmental systolic blood pressure measurements bear some relationship to the hyperaemic index. However, it remains to be seen whether determination of segmental resistance (pressure difference/volume flow) is in practice feasible and whether there is a correlation between high resistance and hypoperfused limb segments Evaluation of segmental perfusion by radioisotope scanning, both after ischaemia[31,32] and during exercise[33-36], has also suggested a relationship between segmental hypoperfusion and the site of arterial occlusion. Angelides[37] quantified this relationship and reported that after exercise the thigh/calf perfusion ratios in both normal limbs and limbs with aortoiliac disease were approximately equal, whereas in limbs with femoropopliteal disease the corresponding ratio was significantly higher. Although duplex ultrasound and radioisotope studies have obvious differences in technique and methodology the conclusions are similar. In both normal subjects and limbs with aortoiliac disease the hyperaemic response in the above and below knee segments is of the same magnitude, whereas in limbs with femoropopliteal disease there is relative hypoperfusion below the knee

In summary, determination of volume flow in the common femoral artery was not an accurate haemodynamic criterion of critical ischaemia, even when measurements were performed after a limited period of circulatory stress. Estimation of peak flow in the common femoral artery after whole limb ischaemia failed to identify the site of arterial occlusion. Measurement of peak flow during hyperaemia of different limb segments enabled calculation of the hyperaemic index This clearly revealed the level of the arterial occlusion

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Impact of duplex scanning on carotid endarterectomy

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Duplex ultrasound permits safe and accurate assessment of the extracranial vasculature. This paper reports the change in patterns of referral to a specialized vascular unit following its introduction, increased referrals were seen in all specialities except neurology. A widely available and reliable duplex service has revealed more extracranial vascular disease than was previously recognized, and has increased referrals for carotid endarterectomy, thereby increasing surgical workload.

Keywords: Atherosclerosis, stroke, duplex ultrasound, carotid endarterectomy

A difference exists between the number of carotid endarterectomies performed in the UK and the numbers performed elsewhere in the world[1]. Extracranial vascular disease might have an increased prevalence abroad, but it is more likely that the discrepancy is due to variations in selection criteria for operation The traditional indication used by British vascular surgeons (on advice from neurologists) has been transient ischaemic attack. This diagnosis is usually based on clinical impression, and extracranial vascular disease is often confirmed using arch angiography. Duplex ultrasound scanning has substantially altered this conservative approach. This paper examines changes in referral patterns and management policy following the introduction of duplex ultrasonography.

Patients and methods

The clinical details of 100 consecutive patients undergoing carotid endarterectomy were collected prospectively Angiography, when performed, was done via the transfemoral route Biplanar views were employed routinely, with selective carotid catheterization Duplex scanning was carried out by experienced physicists, using either a Honeywell Ultra Imager® (Honeywell-Biosound Europe, Diegem, Belgium), or a Sonicaid Vasoview® (Oxford Sonicaid Ltd., Chichester, UK). All operations were performed by A.D.B.C., and a Javid shunt (BARD/USCI Ltd., Crawley, UK) was used whenever possible for cerebral protection

Results

One hundred and seventeen consecutive carotid endarterectomies, in 100 patients, were performed between 1981 and late 1987 (median age 70 years, range 34–84 years); male:female ratio 2·6:1). The median postoperative stay was 4·5 days; the range was from 3 days to 10 months, however, and this skew was due to four patients with stroke who required long-term rehabilitation. There were two deaths (1·7 per cent), one death was due to stroke and the other to a peroperative myocardial infarction. There were four peroperative strokes with permanent neurological deficit, giving an overall stroke/mortality rate of 5·1 per cent for the operation

Table 1 illustrates the cumulative referral rate by source. Access to non-invasive assessment has always been available to all specialties in the hospital. After the introduction of duplex ultrasonography in 1983, referrals for consideration of endarterectomy increased and there was a change in the manner of referral. Increases appeared in all disciplines except neurology. While transient ischaemic attack remained the predominant indication, the numbers of patients with completed strokes and high grade asymptomatic stenoses rose disproportionately (*Table 2*).

The increasing reliance on duplex scanning is illustrated in *Figure 1*. Most patients still had arteriography, especially when validation studies were being carried out, but in 1987 the proportion dropped to 30 per cent[2]. The indication for arteriography in this group was either suspected proximal disease or cerebral symptoms inconsistent with the duplex scan.

Finally, there was no evidence from Hospital Activity Analysis figures that admission for or death rates from cerebrovascular accident had changed significantly during the study period

Discussion

The availability of a duplex scanner in the vascular laboratory coincided with an increase in the number of carotid endarterectomies performed. Although there has been an increase in the number of carotid endarterectomies performed in the UK, there have been no changes in the selection criteria for surgery in this unit. This increase may reflect a growing number of patients with carotid atheroma, but the steady

Table 1 *Number of patients referred for possible carotid endarterectomy according to referral source and year of referral*

	Year						
Referral source	1981	1982	1983	1984	1985	1986	1987*
Neurology	3	2	1	4	1	1	0
Ophthalmology	0	1	0	2	3	3	1
General medicine	0	2	3	10	8	2	3
Cardiology	0	1	2	1	1	1	4
General practice	1	1	1	3	9	11	11
Self	0	0	2	5	4	3	6
Total	4	7	9	25	26	21	25

* Part of year only

Table 2 *Indication for referral according to year*

	Year						
Indication	1981	1982	1983	1984	1985	1986	1987*
Transient ischaemic attack	3	2	1	10	8	9	12
Cerebrovascular accident	1	0	4	4	7	2	6
Amaurosis	0	3	1	3	5	7	2
Asymptomatic	0	0	2	4	3	3	4
Vertebrobasilar	0	1	1	4	2	0	1
Other	0	1	0	0	1	0	0
Total	4	7	9	25	26	21	25

* Part of year only

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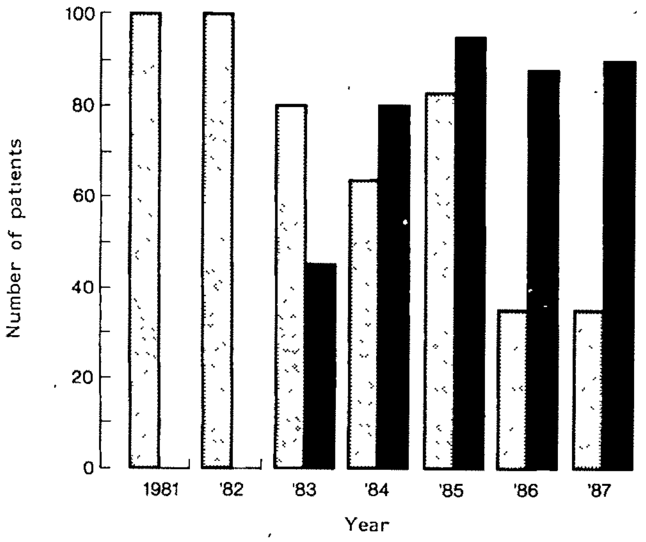

Figure 1 *Number of patients undergoing angiography* (□) *and duplex scanning* (■) *for the years 1981–87*

incidence of admission for and death from cerebrovascular accident during the study does not support this concept

Alternatively, the increase may well reflect the manner in which carotid atheroma is perceived. It is now well known that cervical bruits are unrelated to the extent of carotid disease and might not even be present in severe stenosis[3]. Referring physicians seem to be more impressed by a report of 75–99 per cent carotid stenosis than by hearing a bruit. During the study period, lack of symptoms also became less important and the indications for surgery consequently expanded[4]. Early in this series, all patients were symptomatic, but towards the end an appreciable number of asymptomatic patients had undergone surgery on the basis of high grade or progressive lesions Such a policy has been shown to improve survival[5] Similarly, a number of patients underwent endarterectomy for contralateral stenosis following stroke due to internal carotid occlusion. Previously these patients would not have been referred.

The reliability of duplex ultrasonography is not now in question, and our accuracy is similar to that found in other major centres[6] with a specificity of 85 per cent, a sensitivity of 99 per cent and an overall agreement of 82 per cent with contrast radiology. The technique has achieved a nearly threefold reduction in radiological investigation for suspected carotid lesions according to one recent report[7]. It is the role of routine arteriography that is now in question, especially as intracranial views are seldom required now that extracranial–intracranial bypass is less often advocated[8,9].

Clearly, this review of a single practice is idiosyncratic and sheds no light on whether the surgery performed was actually necessary or will influence the mortality rate from stroke. The role of carotid endarterectomy is as yet uncertain, particularly for asymptomatic patients What does appear clear from this experience, however, is that there was much undocumented extracranial vascular disease in this health district and that the introduction of duplex ultrasonography led to a marked increase in the number of carotid endarterectomies

The results of prospective trials will make the general situation clearer, but as many of the more seriously affected patients might not meet the inclusion criteria, it is optimistic to expect such trials to resolve all the controversies surrounding carotid endarterectomy[8]

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Aortoiliac endarterectomy: an 11-year review

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Fifty-seven patients underwent aortoiliac endarterectomy over an 11-year period, the majority (86 per cent) for disabling claudication. No patient died within 30 days of surgery, but nine patients suffered significant complications. The cumulative survival rate was 98 per cent at 1 year, and was 94 and 78 per cent at 5 and 10 years respectively. Cumulative operated segment patency rates were 92 per cent at 5 years and 68 per cent at 10 years. There was no significant difference in survival rates between patients who smoked after surgery and those who did not, but smokers had significantly worse rates for cumulative patency, limb failure and symptom status than non-smokers. Twenty-seven patients developed worsening symptoms during follow-up and 24 patients required secondary vascular intervention. Fourteen patients subsequently required aortofemoral bypass and the largest single cause of operated segment failure was recurrent disease in the external iliac artery. Our evidence suggests that, while aortoiliac endarterectomy should be considered in young patients with localized disease not involving the external iliac artery, those who do not fit these criteria should be considered for primary aortofemoral bypass. Regardless of the choice of operation, the chance of success is jeopardized if the patient continues to smoke.

Keywords: Aortoiliac endarterectomy, smoking, aortofemoral bypass

Aortoiliac endarterectomy was the most common form of reconstruction of the severely diseased aortoiliac segment before the introduction of aortofemoral bypass. Although a relatively safe procedure, with the advantage of using autogenous tissue, a high incidence of proximal recurrent disease has meant that the majority of patients now undergo aortofemoral bypass, despite the recognized risks of prosthetic complications A retrospective review of aortoiliac endarterectomy has been carried out to see if this policy is justified.

Patients and methods

A retrospective review was undertaken of the case records, operative details and follow-up of a consecutive series of 57 patients who underwent aortoiliac endarterectomy over an 11-year period between January 1974 and December 1984. At the start of the study, nearly all patients with significant aortoiliac disease underwent endarterectomy With increasing use of aortofemoral bypass in subsequent years, however, the indications for endarterectomy have become more selective Initially these included young patients with localized disease not extending below the inguinal ligament. Latterly, however, endarterectomy was employed only if there was no disease distal to the common iliac artery Most patients were regularly reviewed at the vascular clinic after surgery, although for a small number, for whom long distances precluded regular clinic attendance, the family practitioner completed a questionnaire. Follow-up ranged from 5 to 144 months, with a mean of 89 months.

Endarterectomy was performed through a transverse aortotomy and longitudinal iliac arteriotomies using a ring stripper One patient underwent aortic endarterectomy alone In the 109 operated limbs, endarterectomy was limited to the common iliac segment in 19, was extended to incorporate the external iliac artery in 87, and was extended down to the common femoral artery in three. The arteriotomy was extended to the distal aspect of the plaque and, if the distal intima was loose, it was fixed with a 6 0 polypropylene suture to prevent intimal flap elevation. The arteriotomies were closed with 5 0 polypropylene. Eight arteriotomies were closed with a saphenous vein patch, one of these being in a woman with a hypoplastic aortoiliac segment in which a reversed Y-shaped vein graft was inserted

Statistical analysis was by Fisher's exact test, the log rank test with χ^2 analysis and Student's *t* test as appropriate For the purposes of this study, limb patency refers to the continued patency of the operated arterial segment. Patency was determined by clinical examination and/or angiography in those presenting with worsening symptoms. On the other hand, limb failure included not only those patients with occlusion but also those with any degree of recurrent stenosis of the operated segment which required secondary vascular intervention[1]. In those situations where there was recurrent diffuse aortoiliac stenotic disease, the limb(s) that were symptomatic were counted as failures Improved symptom status refers to the maintenance of clinical improvement after surgery Worsening symptoms will therefore include those due to proximal and distal disease progression. The patient who underwent aortic endarterectomy alone has not been included in the analysis of limb patency, failure or symptom status although she has remained asymptomatic with normal pulses throughout follow-up.

Results

Fifty-seven patients, 35 men (age range 38–71 years, mean 52 7 years) and 22 women (age range 38–73 years, mean 53·4 years) underwent aortoiliac endarterectomy in 109 limbs. Three (5 per cent) patients had previously undergone some form of vascular reconstruction and 32 (56 per cent) patients continued to smoke postoperatively. In 49 patients, the indication for operation was disabling claudication; the remainder presented with rest pain (five patients) and ulceration/gangrene (three patients). Infrarenal aortic occlusion was evident in four (7 per cent) patients, and three patients (all female) had evidence of a hypoplastic aortoiliac segment. Sixteen (28 per cent) patients had occlusion of one of the iliac vessels, while the remainder had evidence of severe stenotic aortoiliac disease. Sixteen limbs had preoperative evidence of superficial femoral artery occlusion.

No patients died following aortoiliac endarterectomy, but nine (16 per cent) suffered significant complications (*Table 1*) Two patients suffered acute aortoiliac occlusion in the early postoperative period to give an immediate limb failure rate of 4 per cent. Five patients required further intervention within 30 days of operation A successful aortoiliac thrombectomy was performed in one of the patients with occlusion, the second undergoing an aortofemoral bypass. One patient whose

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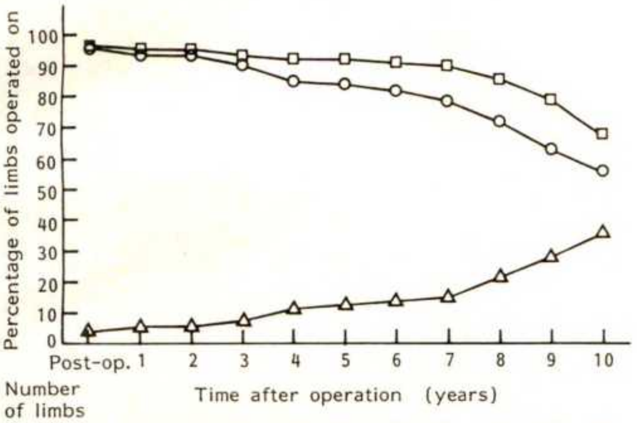
Table 1 *Operative morbidity in nine of 57 patients undergoing aortoiliac endarterectomy*

	No. of patients
General morbidity	
Wound infection	2
Peritonitis	1
Pulmonary embolus	1
Vascular morbidity	
Aortic thrombosis	2
Trash foot	1
Foot drop	1
Haemorrhage	1



Number of limbs	Post-op.	1	2	3	4	5	6	7	8	9	10
□	105	102	95	92	86	83	78	73	62	42	24
○	105	101	94	88	81	79	74	68	55	39	24
△	105	101	94	91	83	81	77	72	59	42	24

Figure 1 *Cumulative rates for operated segment patency, limb failure and clinical outcome in 57 patients undergoing aortoiliac endarterectomy.* □, *limb patency;* △, *failure rate; and* ○, *clinically improved*

preoperative gangrene did not improve after surgery required an above-knee amputation and another required oversewing of a leaking iliac arteriotomy. The remaining patient required a total gastrectomy for proximal gastric infarction after a synchronous highly selective vagotomy for erosive gastritis. Because of the potential risk of contamination at the original operation, the intended aortofemoral bypass was abandoned and an aortoiliac endarterectomy was performed instead. The patient died 5 months after surgery from a stroke.

The cumulative survival rate was 98 per cent at 1 year, 94 per cent at 5 years and 78 per cent at 10 years, the majority of deaths (75 per cent) being of cardiovascular origin. There was no significant difference in long-term survival rates between the sexes or between smokers and non-smokers. The overall results for cumulative rates of limb patency, limb failure and improved symptom status are detailed in *Figure 1*. The cumulative limb patency rates were 92 and 68 per cent at 5 and 10 years respectively. The cumulative limb failure rates were 13 and 36 per cent at 5 and 10 years respectively. Twenty-seven patients developed worsening symptoms during follow-up; the underlying causes are detailed in *Table 2*. Proximal recurrent disease was found to be the underlying cause in 20 (74 per cent) patients, and the most common single cause of failure was recurrent disease in the external iliac artery. Distal disease was the underlying cause in seven (26 per cent) patients, the most common being femoropopliteal occlusion. Twenty-four patients underwent secondary vascular intervention, at which 26 procedures were performed (*Table 3*), the most common being aortofemoral bypass at a mean of 77 months (range 13–132 months) after endarterectomy. Axillofemoral bypass was preferred to aortofemoral bypass in one patient who had previously undergone a renal transplant and an external iliac and common femoral endarterectomy. Of the five patients with femoropopliteal occlusion, only two proceeded to distal bypass. The remaining three had poor run-off vessels below the knee. Only one patient required a major limb amputation during follow-up, for irreversible ischaemia after a common femoral artery embolus.

Rates for cumulative patency, limb failure and symptom status were worse in smokers than in non-smokers. Non-smokers had an operated segment patency of 80 per cent at 10 years, which was significantly better than 61 per cent for smokers ($P<0{\cdot}05$). The cumulative limb failure rate at 10 years was 44 per cent in smokers, signficantly higher than 24 per cent in non-smokers ($P<0{\cdot}05$). Smokers were significantly more likely to develop worsening symptoms requiring secondary surgical intervention than non-smokers ($P=0{\cdot}041$), and only 47 per cent of smokers maintained a cumulatively improved symptom status at 10 years compared with 69 per cent of non-smokers ($P<0{\cdot}05$).

Discussion

In this vascular unit, aortofemoral bypass has virtually replaced endarterectomy in the management of patients with aortoiliac disease (*Figure 2*), although a small number of endarterectomies

Table 2 *Causes of worsening symptoms in 27 patients during follow-up*

Disease	No. of patients
Proximal recurrent disease	
Bilateral non-occlusive aortoiliac disease	3
Bilateral aorto/aortoiliac occlusion	3
Unilateral external iliac occlusion/stenosis	10
Unilateral common iliac occlusion/stenosis	4
Distal vessel disease	
Femoropopliteal occlusion	5
Common femoral embolus	1
Common femoral stenosis	1

Table 3 *Details of 26 secondary procedures in 24 patients*

Procedure	No. of patients
Aortofemoral bypass	14
Common iliac–profunda femoris bypass	2
Common iliac endarterectomy + vein patch	1
Iliac thrombectomy and angioplasty	1
External iliac + common femoral endarterectomy	1
Axillofemoral bypass	1
Femorofemoral bypass	1
Femoropopliteal bypass	2
Phenol sympathectomy	1
Common femoral embolectomy	1
Below-knee amputation	1

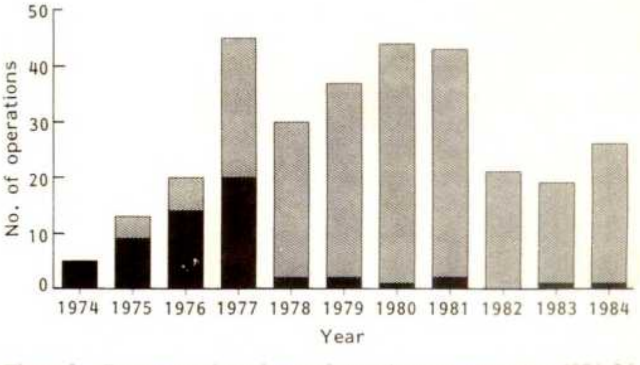


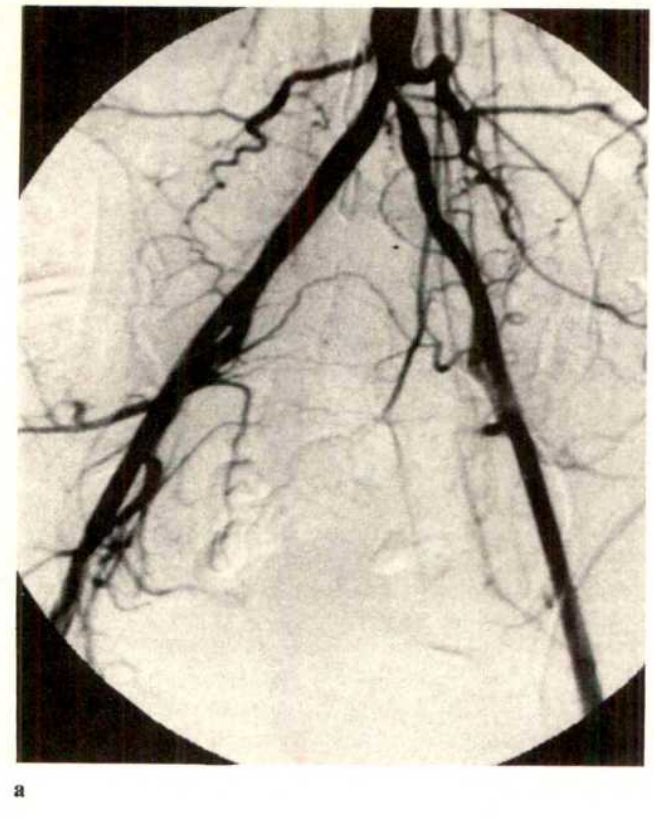
Figure 2 *Frequency of two forms of aortoiliac reconstruction, 1974–84:* ■, *aortoiliac endarterectomy;* ▨, *aortofemoral bypass*

are still performed each year. It is worthy of note, however, that following the introduction of percutaneous transluminal angioplasty in 1981 the annual frequency of aortofemoral bypass also decreased. The advantage of endarterectomy is the avoidance of a prosthesis[1], especially in younger patients with localized disease. The disadvantages include a longer and more technically difficult operation and increased blood loss[2]. Although no record was kept of the procedure time and blood loss for this review, it has been our subjective impression that both were increased compared with aortofemoral bypass. Aortofemoral bypass is a quicker procedure, but involves the insertion of prosthetic material with the subsequent risk of graft-related complications such as sepsis, occlusion and anastomotic aneurysm formation[3]. Our zero operative mortality rate confirms the safety of endarterectomy, and the operative morbidity rate, particularly the incidence of immediate failure, is comparable with the experience of others[1,4].

A significant proportion of our patients has required secondary surgery, primarily because of recurrent proximal disease. The most commonly performed procedure was aortofemoral bypass. In the course of serial angiographic follow-up of patients undergoing aortoiliac endarterectomy, Szilagyi[5] showed that the incidence of restenosis increased with time and that by 10 years 41 per cent of operated iliac arteries had evidence of stenosis compared with an incidence of only 4 per cent in the aorta. In a review of the principle causes of failure following endarterectomy, Darling and Linton[6] suggested that recurrent disease was because of inadequate depth of endarterectomy, errors in arteriotomy closure, failure to carry endarterectomy to the appropriate level, and the presence of unrecognized residual disease, particularly in the external iliac and common femoral arteries. Gaspard *et al.*[2] found that 28 per cent of endarterectomy attempts had to be abandoned, usually because of damage to the external iliac vessels. Recurrent occlusive disease within the external iliac segment was the largest single cause of limb failure in this series and in others[4,7]. Inahara[1] comments that the most important part of endarterectomy is the complete removal of the circular fibres of the media, with less severely diseased segments being the most difficult to endarterectomize. It is generally accepted that the external iliac artery is one of the most difficult vessels in which to achieve a satisfactory endarterectomy because of difficulty in exposure and a more adherent and muscular media than at other sites[4]. Because of this, and because recurrent external iliac disease required reoperation in 20 per cent of limbs by 5 years and 32 per cent by 10 years, Brewster and Darling[4] have suggested that the presence of disease below the common iliac artery is an indication for aortofemoral bypass. This viewpoint is not held by everyone, particularly Inahara, who has developed the eversion endarterectomy method[1] and has successfully employed it in the management of patients with all grades of aortoiliac and distal vessel disease.

In the present series, cumulative limb failure and clinical outcome generally mirrored the deterioration in operated segment patency. The cumulative limb failure rate is slightly higher than the occlusion rate because the former includes a small number of recurrent stenoses requiring surgical intervention. Similarly, the clinical outcome is worse than either the patency or failure rates because it takes into account worsening symptoms due to distal disease progression.

It would seem therefore that, while aortoiliac endarterectomy is a relatively safe procedure with good cumulative patency rates and clinical outcome, a significant proportion of patients will require secondary proximal reconstruction. Direct comparisons of the results of aortoiliac endarterectomy and aortofemoral bypass have been made[2,4,8], although few contain randomized patients[2] and so the results are not easy to interpret. In Aberdeen Royal Infirmary, aortofemoral bypass has an overall operative mortality of 2·4 per cent, a cumulative 5-year patency of 87 per cent, and an incidence of graft infection of 1·6 per cent[3]. Only 60 per cent of patients, however, reported an



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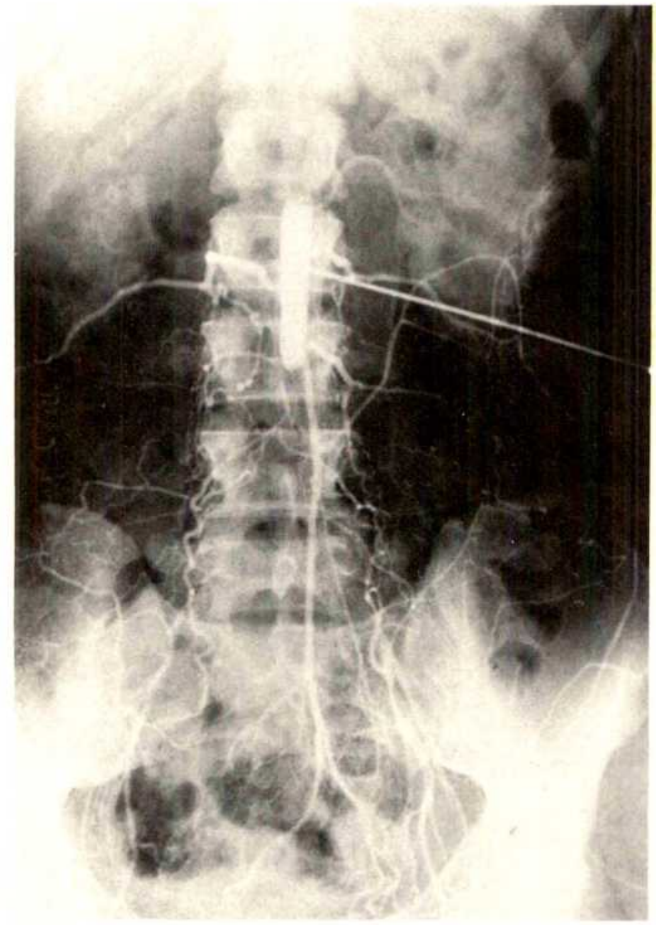

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Figure 3 *Current indications for aorotiliac endarterectomy. Preoperative angiograms of suitable patients: (a) non-occlusive disease primarily affecting the distal aorta and left common iliac artery in a 40-year-old man; and (b) infrarenal occlusion of the aorta in a 39-year-old woman*

improved clinical outcome at 5 years compared with 84 per cent of those undergoing aortoiliac endarterectomy in this series. While aortofemoral bypass may not seem to confer any overall benefit, there were considerable differences between the two populations. Aortofemoral bypass patients were significantly older (mean age 59·8 years: $P<0{\cdot}05$), 57 per cent of limbs had preoperative evidence of distal occlusive disease, and 29 per cent of patients had initially presented for limb salvage. All of these factors predispose to a worse clinical outcome[3]. The commonest cause of limb failure in the endarterectomy group was proximal recurrent disease and the commonest cause of limb failure in bypass patients was graft occlusion secondary to pre-existing or progressive distal occlusive disease[9].

Our current indications for aortoiliac endarterectomy are similar to those of Brewster and Darling[4] and Duncan *et al.*[8]. Patients under the age of 55 years with localized aortoiliac disease not involving the external iliac artery are considered for endarterectomy (*Figure 3*). The advantage of using autogenous tissue in these young patients is considered important and they can always be offered aortofemoral bypass in the future. In this series, the need for aortofemoral bypass was delayed by a mean of 77 months by endarterectomy. Older patients, and those with disease involving or distal to the external iliac artery, are considered for primary aortofemoral bypass. These criteria mean that currently only about 20 per cent of those patients who underwent aortoiliac endarterectomy during the period of this study would now be considered for endarterectomy.

Regardless of the choice of procedure, patients must recognize that a significant factor in their clinical outcome will be the decision to continue smoking after surgery. Smoking significantly worsened cumulative patency and limb failure rates and influenced the likelihood of secondary surgery. It is worthy of note that nearly 70 per cent of patients remained clinically improved at 10 years provided they refrained from smoking, while only 47 per cent of smokers remained clinically improved at this time.

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Simultaneous aortic and renal artery reconstruction

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Nine patients presenting with combined aortic and renal artery disease underwent simultaneous infrarenal aortic reconstruction and renal revascularization. Seven patients had aneurysmal and two had occlusive aortic disease in association with unilateral (four cases) or bilateral (five cases) atheromatous renal artery stenosis. The indications for renal revascularization were hypertension (n = *8*) *refractory to medical treatment or associated with renal functional impairment and chronic renal failure alone* (n = *1*). *Five patients developed postoperative complications with one fatality. Eight patients were followed up for between 7 months and 4 years. Control of blood pressure had improved in six of seven hypertensive patients. Serum creatinine levels were stabilized or had fallen in five patients. Simultaneous aortic and renal artery reconstruction is widely recognized as having a high postoperative morbidity rate but can improve control of hypertension and stabilize renal function in carefully selected patients.*

Keywords: Aortic disease, renal artery disease, reconstructive vascular surgery

Atheromatous renal artery stenosis is common in patients with peripheral vascular disease. In a series of patients with peripheral vascular symptoms studied arteriographically, 60 (40 per cent) of 149 renal arteriograms obtained incidentally showed unilateral or bilateral renal artery stenosis of at least 50 per cent[1]. Arteriograms performed in 169 patients with abdominal aortic aneurysms demonstrated that 37 (22 per cent) had renal artery stenosis[2]. It seems, however, that less than 5 per cent of patients undergoing aortic reconstruction or bypass have simultaneous renal revascularization[3,4].

Whereas the indications for surgery to the infrarenal aorta are relatively well defined, those for reconstruction of renal artery stenosis are controversial. Although Hunt and Strong's prospective study of patients with renovascular hypertension seemed to indicate significantly better results from surgical compared with medical therapy at 7- and 14-year follow-up[5], there are no published details of any randomized prospective trial of surgical *versus* medical therapy. A surgical approach may be indicated in patients with 'difficult' renovascular hypertension, i.e. that which is poorly controlled by medical treatment or where antihypertensive therapy is likely to result in deterioration of renal function. Recently there has been increasing interest in revascularization to improve or preserve renal function impaired or threatened by ischaemia[6,7]. This may be an additional factor in the decision to treat surgically a patient with renovascular hypertension or may be the sole indication for renal artery reconstruction in selected patients.

When surgery is indicated for disease of the infrarenal aorta, the presence of difficult hypertension or impaired renal function due to renal ischaemia may suggest the need to consider simultaneous aortic and renal artery reconstruction. Reports from North America[3,8–13] have demonstrated that this procedure can be successfully performed. We describe our experience with simultaneous aortic and renal artery reconstruction in nine patients.

Patients and methods

Between May 1984 and May 1988, nine patients underwent simultaneous aortic reconstruction and renal revascularization (*Table 1*). Three patients had unilateral and five had bilateral high grade atheromatous renal artery stenoses. One patient had stenosis of the artery to a solitary kidney, the contralateral non-functioning kidney having been excised 9 months previously. Five patients presented with hypertension and three with the symptoms of aortic disease. The remaining patient, referred by a nephrologist because of an abdominal aortic aneurysm, was normotensive but had chronic renal failure. The renal physician considered that this patient was likely to require haemodialysis within 12 months. Evidence of diffuse arterial disease was common. Carotid artery disease was present in six patients, three of whom were symptomatic and required carotid endarterectomy. Two patients had symptoms of ischaemic heart disease and a further four had ECG abnormalities (inferolateral ischaemia, 2; left ventricular hypertrophy, 1; and right bundle branch block, 1). Two patients were hyperlipidaemic and three smoked cigarettes. Seven of the patients had an elevated serum creatinine concentration and a creatinine clearance below 65 ml/min (*Table 2*). The three patients with unilateral renal artery stenosis had renal vein renin ratios of 1·5, 1·6 and 2·6 lateralizing to the side of the stenosis.

A standard operative approach through a midline incision was used and the diseased vessels were exposed and controlled. In eight patients, a composite graft of USCI Sauvage Bionit material (Bard Europe Limited, Haywards Heath, UK) was constructed on the bench by suturing side branches of 5–8 mm diameter to a straight ($n = 2$) or the stem of a bifurcated ($n = 6$) aortic graft. The graft was preclotted prior to giving the patient 5000 units heparin intravenously. The anastomoses were then constructed in the following locations: aortic with unilateral renal ($n = 1$), aortoiliac with unilateral renal ($n = 2$), aortofemoral/popliteal with unilateral renal ($n = 1$), aortic with bilateral renal ($n = 1$), aortoiliac with bilateral renal ($n = 1$) and aortofemoral with bilateral renal ($n = 2$). *Figure 1* shows the composite graft constructed for patient 6, who had an accessory lower polar renal artery on the right, and the graft sutured in place. In the remaining patient straight aortic graft replacement was accompanied by endarterectomy and Sauvage patch angioplasty of each renal artery. Before clamping of a renal artery, core-cooling of the kidney was achieved using a perfusate of 500 ml 5 per cent dextrose, 20 mg lignocaine, 20 mg frusemide and 2500 units heparin at 4°C. The core-cooled ischaemic times of the kidneys ranged from 16 to 100 min (median 55 min).

Following surgery, renal function was closely monitored. Six of the patients had renal angiography (five by digital subtraction) between postoperative days 7 and 23 (median day 10). Postoperative complications in patients 3, 8 and 9 prevented renal arteriography. After discharge from hospital the patients were kept under regular outpatient review. The length of follow-up ranged from 7 months to 4 years (median 2 years 2 months). The response of the patient's hypertension to surgical revascularization was assessed by a modification of the criteria suggested by Geyskes *et al.*[14]:

Cured = diastolic blood pressure 90 mmHg or less on no medication.

Improved = diastolic blood pressure 91–109 mmHg and a decrease of 15 per cent or more compared with the preoperative level; or diastolic

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Table 1 *Arteriographic findings and indications for renal revascularization*

Patient no.	Age	Sex	Arteriographic findings	Indications for renal revascularization
1	73	M	Aortoiliac aneurysm Right renal artery stenosis	Hypertension
2	64	M	Aortic aneurysm Left renal artery stenosis	Hypertension, impaired renal function
3	66	F	Aortoiliac aneurysm Right renal artery stenosis. Left renal artery arising from aortic aneurysm	Difficult hypertension, impaired renal function
4	66	F	Aortoiliac aneurysm Left renal artery stenosis (previous right nephrectomy)	Difficult hypertension, impaired renal function
5	59	M	Aortic aneurysm Bilateral iliac and left superficial femoral artery occlusion Bilateral renal artery stenosis	Difficult hypertension, impaired renal function
6	43	M	Aortic occlusion at the level of 1st lumbar vertebra Bilateral renal artery stenosis	Difficult hypertension, impaired renal function
7	49	M	Aortoiliac stenosis Bilateral renal artery stenosis	Difficult hypertension
8	64	M	Aortic aneurysm Bilateral renal artery stenosis	Difficult hypertension, impaired renal function
9	61	M	Aortic aneurysm. Bilateral renal artery stenosis	Chronic renal failure

Table 2 *Results of renal investigations*

Patient no.	Serum creatinine (μmol l^{-1})	Creatinine clearance (ml min^{-1})	Renal vein renin (ng ml^{-1} h^{-1})			^{99}Tc DMSA scan	
			RRV	LRV	IVC	Right kidney (%)	Left kidney (%)
1	114	Not measured	2·9	1·1	1·7	41	59
2	141	63	5·3	8·0	5·2	56	44
3	136	20	3·4	1·9	2·5	25	75
4	135	46	Not measured			Not performed	
5	155	32	13·1	5·1	4·6	50	50
6	148	36	>75	>75	>75	52	48
7	91	82	2·1	2·7	1·8	78	22
8	142	35	66·5	83·3	40·3	38	62
9	525	16	1·0	0·9	0·8	70	30

RRV, right renal vein; LRV, left renal vein; IVC, inferior vena cava

blood pressure 91–109 mmHg, a decrease of 10 per cent compared with the preoperative level and discontinuation of at least one drug; or diastolic blood pressure 90 mmHg or less and discontinuation of at least one drug.

Results

Four patients made an uneventful recovery following surgery. Five developed postoperative complications and one (patient 3) died from colonic infarction possibly related to ligation of aneurysmal internal iliac arteries. The serum creatinine remained within 20 per cent of the preoperative value in four patients (*Table 3*), decreased by over 20 per cent in one patient and increased by over 20 per cent in three patients. The digital subtraction angiogram of patient 5 demonstrated only one of the bilateral renal artery grafts.

Patients 4 and 5 had transient postoperative deterioration in renal function although neither required dialysis. Patient 4 had an episode of coagulase-positive staphylococcal septicaemia 24 days after operation. This organism was also cultured from an infected venous cannulation site. An ^{111}indium-labelled white blood cell scan did not show any focal accumulation of white blood cells in the region of her vascular graft. She made a complete recovery and has had no recurrence of fever in the 8-month period of follow-up. Patient 5 died from acute on chronic respiratory failure 4 years after the surgical procedure.

Right femoral embolectomy of an *in situ* vein bypass graft immediately after initial surgery in patient 8 was successful. He required ventilatory support and intravenous hydralazine therapy during the first seven postoperative days. Patient 9 suffered a progressive deterioration in renal function despite the apparent technical success of this procedure.

At the most recent outpatient review the control of blood pressure was considered to have improved in six of the seven hypertensive patients. Five of the seven patients required an increase in their antihypertensive drugs during the course of their follow-up (*Table 4*).

Patient 8 suffers from left calf claudication at 800 m due to pre-existing occlusive disease of the superficial femoral artery. None of the other patients has complaints attributable to peripheral vascular insufficiency or to the repair of an aortic aneurysm.

Discussion

Several factors influence the decision to recommend simultaneous renal revascularization to a patient who requires surgery for infrarenal aortic disease. Since renal artery stenosis is common in such patients, there must be evidence to suggest that renal ischaemia is of significance in causing hypertension or impairing renal function and that surgical treatment is the appropriate therapy. Simultaneous correction of aortic and renal artery disease should have an acceptable outcome in terms

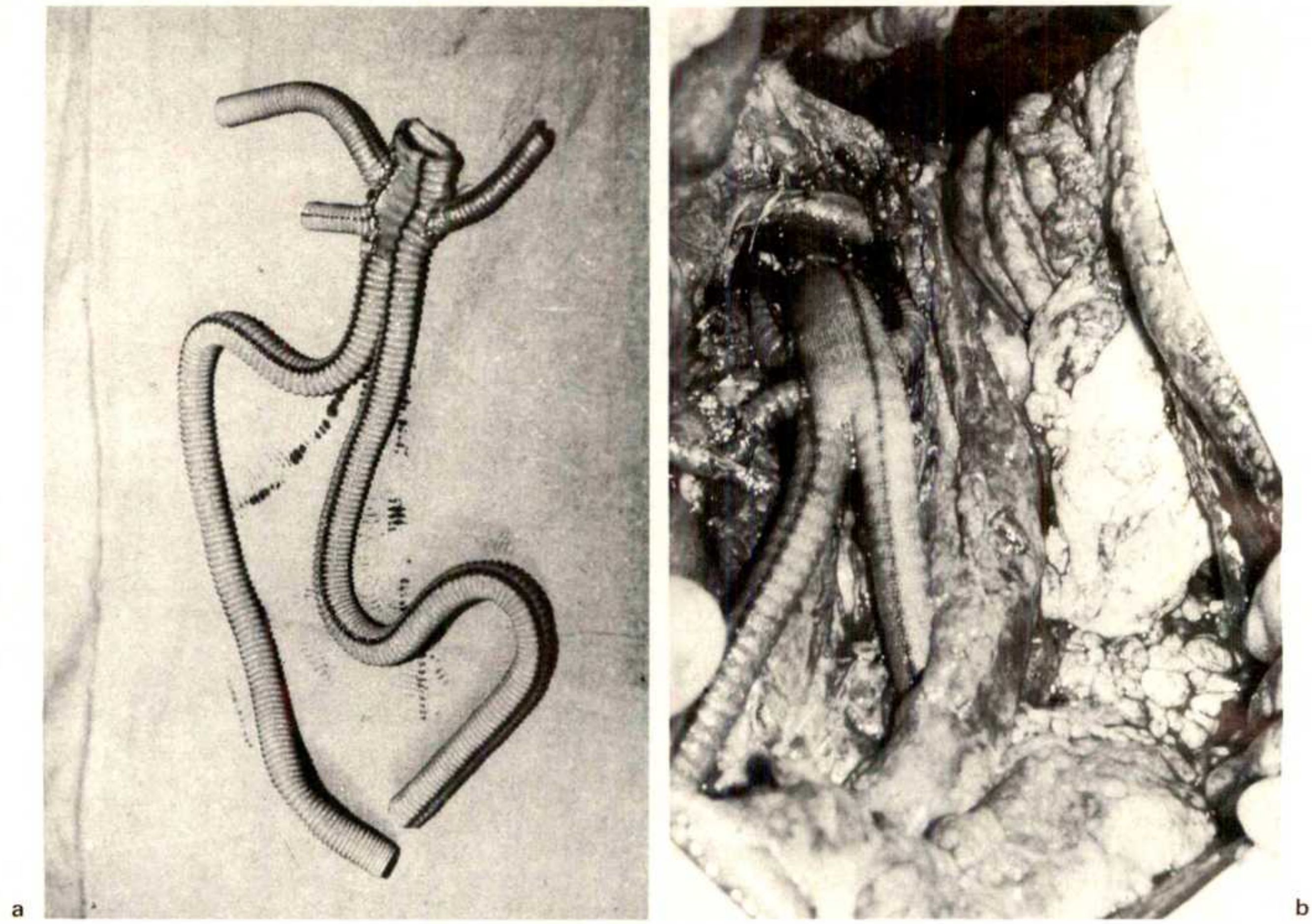

Figure 1 *The composite graft used in patient 6 constructed on the bench,* **a**, *and sutured in place,* **b**

Table 3 *Serum creatinine and arteriographic findings following operation*

Patient no.	Serum creatinine (μmol l^{-1})	Arteriographic findings
1	101	Patent right renal artery graft
2	128	Patent left renal artery graft
4	136	Patent left renal artery graft
5	226	Patent right renal artery graft, left renal artery graft not visualized
6	183	Patent bilateral renal artery grafts
7	79	Patent bilateral renal artery grafts
8	101	Not performed
9	1021	Not performed

of control of hypertension, stabilization or improvement in renal function, postoperative morbidity and mortality.

An intravenous digital subtraction angiogram (DSA) of the abdominal aorta and its branches is now routinely performed before elective repair of an abdominal aortic aneurysm and in those patients with hypertension who would previously have had intravenous urography, i.e. patients under the age of 40 years, patients with a history of renal symptoms or disease and patients over the age of 40 years whose hypertension has proved difficult to control[15]. By specifically requesting late views, a pyelogram is also obtained. If a patient proves to have renal artery disease for which revascularization is indicated, a conventional renal arteriogram is performed before operation to provide optimal definition of the renal vasculature.

To assess the significance of renal artery stenosis in our hypertensive patients, renal vein renin assay and ^{99}Tc DMSA scanning was undertaken. The latter has been shown to correlate well with divided renal creatinine clearance measured by ureteral catheterization[16]. The three patients in our series with unilateral renal artery stenosis and a normal renal artery on the contralateral side had renal vein renin ratios which suggested that renin hypersecretion on the affected side was the cause of their hypertension. The ^{99}Tc DMSA scan results suggested reduced function of the compromised kidney. In the four hypertensive patients with radiological evidence of bilateral renal artery stenosis, none of the kidneys showed evidence of suppressed renin secretion relative to the renin concentration in the inferior vena cava. Although it is difficult to measure the significance of renal artery stenosis when it is bilateral or affects the artery to a solitary kidney, we regarded the presence of difficult hypertension and impaired renal function as important considerations in our decision to revascularize the kidneys. Dean *et al.* found bilaterality of reconstructable disease and a serum creatinine of over 265 μmol/l to be predictors of a significant improvement in renal function in hypertensive patients following revascularization[17].

Medical treatment may fail to control renovascular hypertension adequately and jeopardize renal function. In a series of 41 unselected patients with atheromatous renal artery stenosis whose hypertension was managed medically, Dean *et al.*[18] noted an increase of between 25 and 120 per cent in serum creatinine concentration in 19 (46 per cent) of the patients and progression of stenosis to total occlusion in four patients over a mean follow-up period of 25 months. In six of our eight hypertensive patients control of blood pressure by pharmacological means had been unsatisfactory. Angiotensin converting enzyme inhibitor drugs were not used in the four patients with bilateral renal artery stenosis and the patient with a solitary kidney because of the risk of inducing acute renal failure[19]. Ying *et al.*[20] have suggested that medical treatment of such patients is

Table 4 *Blood pressure and antihypertensive therapy*

Patient no.	Before surgery		At discharge		At most recent review		Length of follow-up
	BP	Therapy	BP	Therapy	BP	Therapy	
1	195/95	Nifedipine 60 mg Cyclopenthiazide 250 μg	178/72	Nifidepine 40 mg	136/74	Nifedipine 40 mg	3 years
2	152/84	Acebutolol 400 mg Nifedipine 80 mg Hydrochlorothiazide 100 mg Amiloride 5 mg	120/80	None	158/84	Nifedipine 40 mg	1 year 4 months
4	166/86	Atenolol 200 mg Nifedipine 40 mg Frusemide 40 mg Amiloride 5 mg	120/70	Atenolol 50 mg	174/86	Atenolol 100 mg Chlorthalidone 25 mg	8 months
5	192/106	Prazosin 16 mg Nifedipine 80 mg Frusemide 40 mg Spironolactone 100 mg	160/90	Nifedipine 40 mg Frusemide 40 mg	162/95	Metoprolol 100 mg Nifedipine 120 mg Frusemide 160 mg	4 years
6	210/120	Prazosin 8 mg Nifedipine 40 mg	180/100	Methyldopa 500 mg Nifedipine 40 mg	180/105	Enalapril 5 mg Nifedipine 80 mg Frusemide 250 mg	3 years 10 months
7	196/116	Nifedipine 60 mg Indapamide 2·5 mg	160/100	Nifedipine 40 mg	126/94	Atenolol 100 mg Chlorthalidone 25 mg	3 years
8	190/95	Atenolol 100 mg Minoxidil 10 mg Frusemide 240 mg	156/76	Atenolol 100 mg Nifedipine 40 mg Chlorthalidone 25 mg	148/72	Atenolol 100 mg Nifedipine 40 mg Chlorthalidone 25 mg	7 months

BP, supine blood pressure; therapy, total daily dose of drugs

particularly likely to result in deterioration of renal function.

Percutaneous transluminal renal angioplasty (PTRA) was not considered appropriate in patients who had either an aortic aneurysm or bilateral ostial stenoses associated with severe aortic atheroma. Geyskes *et al.*[14] have cautioned against the application of PTRA to patients with such lesions. Two of their 44 patients with atheromatous renal artery disease developed cholesterol embolism following PTRA resulting in death or loss of a limb. Both patients had severe aortic atheroma. Brawn and Ramsay[21] found PTRA to be technically unsatisfactory in 12 of 20 consecutive patients who were referred to their hypertension clinic and found to have atheromatous renal artery disease. From a review of previous publications, they suggested that as few as 8 per cent of patients with atheromatous renovascular disease benefit from PTRA.

At the most recent review, blood pressure control had improved in all but one (patient 6) of our seven surviving hypertensive patients using criteria similar to those of Geyskes *et al.*[14] and Brawn and Ramsay[21]. The serum creatinine concentration had remained stable or decreased in five. Patient 9 who underwent renal revascularization for chronic renal failure did not benefit from this procedure but, in common with the seven other surviving patients, has had a satisfactory result from aortic reconstruction.

The postoperative morbidity and mortality rates of simultaneous aortic and renal artery reconstruction may be higher than those of the separate procedures. Dean *et al.*[9] reported a mortality rate of less then 3 per cent for elective repair of an infrarenal aortic aneurysm and less than 1 per cent for renal artery reconstruction but they reported a 12 per cent mortality rate following the combination of these procedures. These authors identified the five important factors in predicting a fatal outcome: 'complex procedures' (including bilateral renal revascularization); elevated serum creatinine concentration ($>265\ \mu\text{mol}\ l^{-1}$); aortic aneurysm repair; electrocardiographic evidence of myocardial ischaemia; and a history of diffuse vascular disease.

In six other studies of simultaneous procedures, postoperative mortality rates have ranged from 3 to 10·3 per cent[3,8,10–13]. Non-fatal complications, mainly renal and cardiovascular, were common in the series with the lowest mortality rates[10,13], 22 complications in 61 patients and seven complications in 32 patients respectively. In the latter series only nine patients had aortic aneurysms. Of the 89 patients reported by Tarazi *et al.*[12], 56 had aortic aneurysms, 33 had bilateral renal artery stenosis and 30 had an elevated serum creatinine. Thirty patients had postoperative complications and there were nine deaths.

In our own series of nine patients the risk factors described by Dean *et al.*[9] were common: seven had aortic aneurysms and six had either bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. In a patient population of this type, the larger experience of the North American centres would have predicted a high rate of postoperative complications demanding the ready availability of intensive therapy and nephrology services. Control of hypertension was improved in six and renal function stabilized in five of our patients, and we consider that our approach to simultaneous aortic and renal revascularization has had an acceptable outcome.

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Effect of acute starvation on plasma fibronectin response to sepsis

There is evidence that undernutrition may contribute to the reduction in plasma fibronectin concentration and the depression of the reticuloendothelial (RE) system associated with severe sepsis. We have investigated the effects of fasting, surgical trauma and sepsis on plasma fibronectin concentrations and RE function. In experiment 1, plasma fibronectin was measured in rabbits ($n = 14$) *before and 48 h after fasting. In experiment 2, sepsis was induced by devascularization of the appendix in animals on a normal diet (sepsis group,* $n = 7$) *and in fasted animals (fasting and sepsis group,* $n = 7$). *A third group of animals underwent only a laparotomy (laparotomy only group,* $n = 7$). *Plasma fibronectin concentrations and the blood clearance and organ distribution of* ^{99m}*technetium tin colloid (TTC) were measured 24 h after operation. Compared with pooled reference plasma, fasting in experiment 1 resulted in a reduction in mean(s.e.m.) plasma fibronectin concentration from 98(1·5) per cent to 86(3·7) per cent* ($T = 2$, $P < 0.005$). *Mean(s.e.m.) plasma fibronectin concentration was raised in the sepsis group to 117(4·6) per cent, compared with 97(2·5) per cent in the laparotomy only group* ($U = 5$, $P < 0.02$), *but there was no such increase in the fasting and sepsis group. There was a delay in the blood clearance and reduced hepatic uptake of TTC in both sepsis groups. The dissociation between fibronectin concentrations and RE function in animal models of sepsis casts doubt on the importance of fibronectin in RE function.*

Keywords: Fibronectin, reticuloendothelial system, intra-abdominal sepsis, nutrition

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Undernutrition is a common problem in surgical patients[1] and is said to have wide ranging effects on both humoral and cellular aspects of immune function, including the impairment of neutrophil and macrophage phagocytosis and a reduction in complement levels. Impairment of reticuloendothelial (RE)-dependent clearance of bacteria[2] and of non-bacterial particulate matter[3,4] have been demonstrated during acute starvation. The mechanisms underlying the RE depression associated with malnutrition are unclear but may include inadequate opsonization, failure of intrinsic phagocytic cell function, and alteration in hepatic blood flow.

Plasma fibronectin may be an important non-specific opsonin for the RE clearance of particulate matter and bacteria. Several workers[5–7] have reported a fall in the concentration of fibronectin in healthy human subjects after a period of starvation. Low plasma fibronectin concentrations accompany severe sepsis[8] and fibronectin may be important for the prevention of dissemination of bacteria and/or products of bacterial sepsis into the general circulation, leading to systemic effects and organ failure. In contrast to man, animal models of sepsis often have raised plasma fibronectin concentrations despite depression of RE phagocytic function[9,10].

In this study a rabbit model was used to investigate the effects of fasting, surgical trauma and sepsis on plasma fibronectin concentrations and RE phagocytic function using ^{99m}technetium tin colloid (TTC) as the RE test agent[11].

Methods

There were two experiments. Male New Zealand white rabbits (2·5–3·0 kg) were used in both.

Animal groups

Experiment 1. Fourteen animals were used. All food was withdrawn for 48 h but free access to water was allowed. Animals were weighed and blood was taken by intracardiac puncture for plasma fibronectin estimation at zero time and 48 h after fasting.

Experiment 2. There were three groups. In the first group, seven of the fasted animals from experiment 1 underwent induction of sepsis by devascularization of the appendix. The second and third groups each contained seven animals on normal diets and these animals underwent either devascularization of the appendix or a laparotomy with handling of the small bowel and appendix. The three groups in this experiment were named: fasting and sepsis, sepsis, and laparotomy only. RE function was measured 24 h after operation. Blood was taken for plasma fibronectin estimation by intracardiac puncture immediately before each animal was killed.

Septic model

Peritonitis was induced in the rabbit by devascularization of the appendix. Animals were anaesthetized with intravenous sodium pentobarbitone and a midline laparotomy performed. The arcade of vessels between the appendix and small bowel and the main appendicular artery and vein were ligated and divided. The appendix was left *in situ* and the abdomen closed.

Plasma fibronectin assay

Blood for plasma fibronectin estimation was collected in paediatric size ethylene diamine tetra-acetic acid-treated polystyrene tubes, centrifuged immediately and the plasma removed for storage at −70°C. Plasma fibronectin concentrations were assayed by an immunoturbidimetric method using commercially available antiserum[12]. The results were expressed as a percentage of the mean value of pooled reference plasma from six rabbits kept under the same conditions as the test animals.

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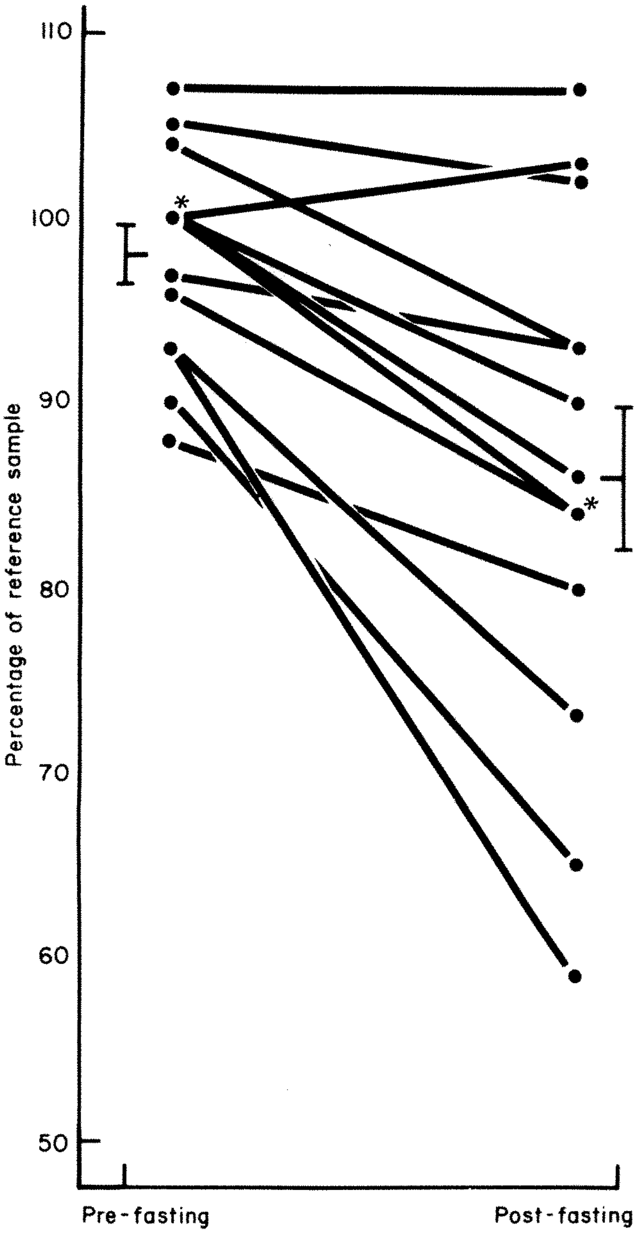

Figure 1 *Plasma fibronectin values (as percentage of reference sample) before and 48 h after fasting.* $P<0{\cdot}005$, *Wilcoxon matched pairs signed rank test.* *—* *represents two animals*

Measurement of RE function

The rate of clearance of TTC from the bloodstream and its uptake into the liver, spleen, lungs and bone were determined. Animals were lightly anaesthetized with intravenous sodium pentobarbitone and a 1 ml bolus of TTC (Amerscan Hepatate II, Amersham International Plc, Amersham, UK) was injected rapidly via an ear vein. The dose of TTC was approximately 0·0002 mg kg^{-1} labelled with 3·7 MBq ^{99m}technetium. Serial blood samples were taken over 45 min from a vein in the opposite ear. Animals were killed with an overdose of anaesthetic and the liver, spleen, right femur and lungs removed. The activity in the blood and organs was measured using a LKB-Wallac (LKB Instruments, South Croydon, UK) 80 000 gamma counter. Blood clearance curves were constructed and analysed using a Hewlett Packard desk-top computer (HP9845B) running a pharmacokinetic program modified to correct for radioactive decay and incorporating statistical analyses. The half-life of the clearance of TTC from the bloodstream was calculated from the first and fastest component of clearance. Uptake of TTC by the organs was measured by counting aliquots of homogenized liver and lung, the whole spleen, and right femur, in the gamma counter using 1 ml TTC as a standard. The results were expressed as a percentage of the injected dose per gram of tissue (per cent ID g^{-1}).

Statistical analysis

Results are expressed as the mean and standard error of the mean. Significance is tested by the Wilcoxon matched pairs signed rank (parameter T) or Mann–Whitney U (parameter U) test.

Results

Experiment 1

Weight change. All 14 animals lost weight during the 48 h fast and this ranged from 4 to 14 per cent (median 8 per cent) of the pre-fasting body weight ($T=0$, $P<0{\cdot}01$).

Plasma fibronectin. Plasma fibronectin results are shown in *Figure 1*. There was a significant reduction in the mean(s.e.m.) concentration of plasma fibronectin after fasting to 86(3·7) per cent, compared with the pre-fasting value of 98(1·5) per cent ($T=2$, $P<0{\cdot}005$).

Experiment 2

Plasma fibronectin. The plasma fibronectin results for the laparotomy only, sepsis, and fasting and sepsis groups are shown in *Figure 2*. The results for the fasting and sepsis group are also shown, along with their pre- and post-fasting values, in *Figure 3*. There was a significant increase in concentration of plasma fibronectin in the sepsis group to a mean(s.e.m.) of 117(4·6) per cent compared with the laparotomy only and fasting and sepsis groups, for which the analogous values were 97(2·5) per cent and 89(4·8) per cent respectively ($U=5$, $P<0{\cdot}02$ and $U=2$, $P<0{\cdot}005$ respectively). The induction of sepsis in fasted animals resulted in a small increase in plasma

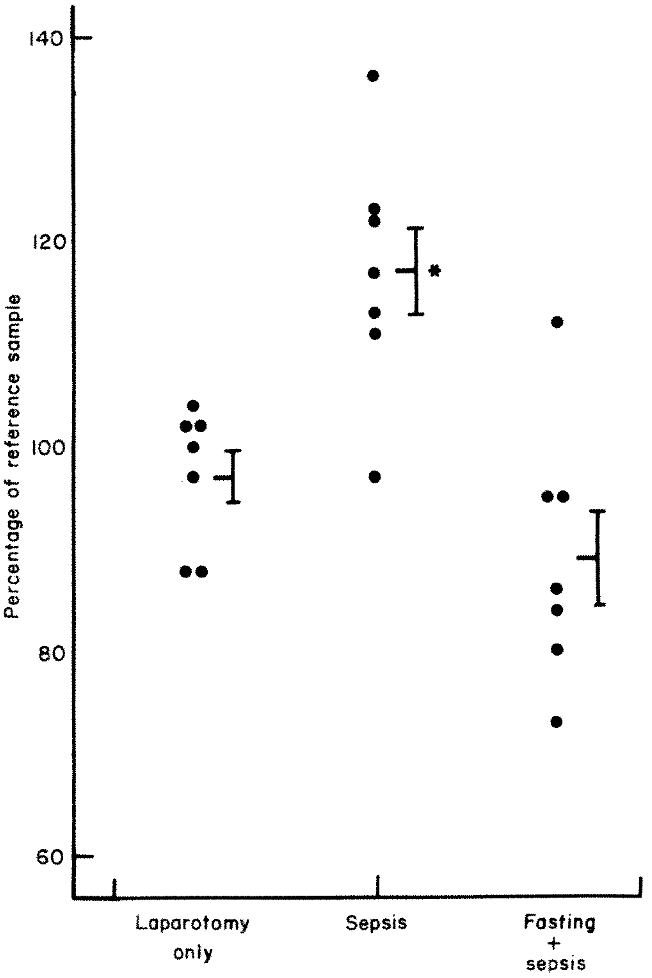

Figure 2 *Plasma fibronectin values (as percentage of reference sample) for the laparotomy only, sepsis, and fasting and sepsis groups.* *$P<0{\cdot}02$, *Mann–Whitney* U *test, compared with laparotomy only group*

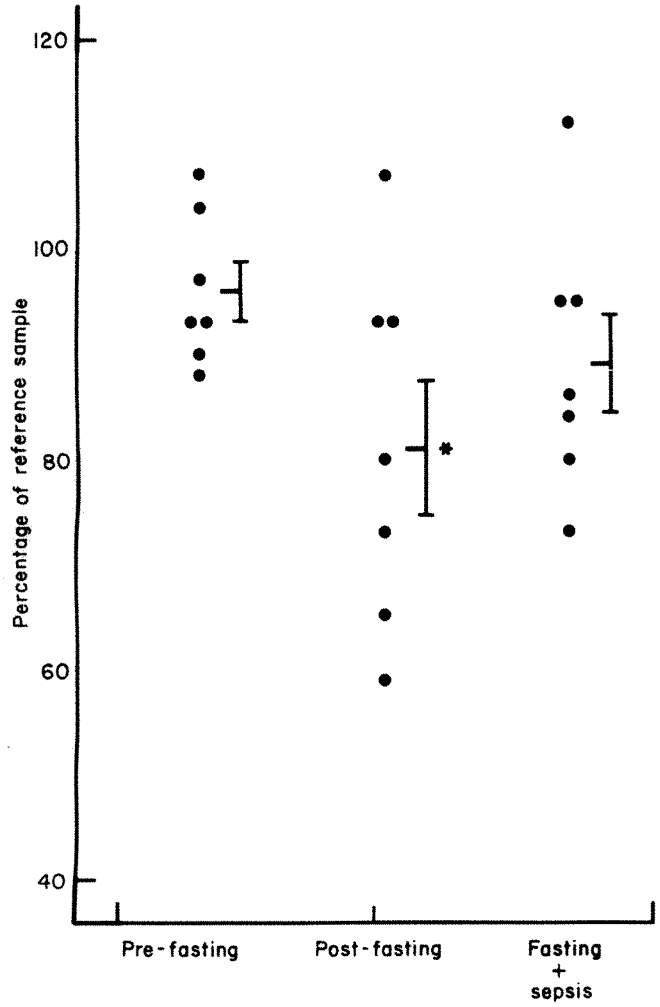

Figure 3 *Plasma fibronectin values (as percentage of reference sample) pre-fasting, post-fasting and 24 h after the induction of sepsis.* *$P<0{\cdot}005$, *Wilcoxon matched pairs signed rank test, compared with pre-fasting value*

fibronectin (*Figure 3*) but this change was not statistically different from the post-fasting value.

Clearance kinetics. The clearance kinetics of TTC from the bloodstream are shown in *Figure 4*. There was a significant delay in the blood clearance of TTC, as shown by the increase in the half-life, in both sepsis groups when compared with the laparotomy only group. The mean(s.e.m.) half-life in the laparotomy only group was 0·74(0·07) min. The analogous value in the sepsis group was 1·50(0·21) min ($U=4$, $P<0{\cdot}01$) and in the fasting and sepsis group was 1·34(0·26) min ($U=6$, $P<0{\cdot}02$).

Organ distribution. The distribution of TTC to the liver, spleen, lungs and bone is shown in *Figures 5* and *6*. The mean(s.e.m.) uptake of TTC by the liver was significantly reduced in the sepsis, and fasting and sepsis groups, being 0·74(0·07) per cent and 0·78(0·03) per cent respectively, compared with that in animals which underwent laparotomy only where the mean uptake was 0·96(0·06) per cent ($U=7$, $P<0{\cdot}05$).

There was a significant increase in the mean(s.e.m.) uptake of TTC into bone in both sepsis groups: sepsis = 0·07 (0·006) per cent, $U=3$, $P<0{\cdot}005$; fasting and sepsis = 0·08 (0·005) per cent, $U=0$, $P<0{\cdot}001$; laparotomy only = 0·04 (0·003) per cent. There was no difference in the splenic or pulmonary localization of TTC between any of the groups.

Discussion

Fasting in rabbits resulted in a reduction in plasma fibronectin to 86 per cent of the pre-fasting value. Similarly starvation in normal human volunteers has been shown to lower the circulating fibronectin concentration[5–7]. In the most recent of these studies[7], plasma fibronectin values decreased after 48 h starvation and continued to fall during the starvation period of 7 days to 58 per cent of the pre-starvation value. On re-feeding, fibronectin concentrations returned to normal within 5 days. Dillon *et al.*[4] demonstrated fibronectin deficiency in rats within 48 h, progressing over 5 days of starvation to 62 per cent of control levels. This change was associated with a depression in RE function, reflected by a prolonged blood retention and decreased hepatic (Kupffer cell) uptake of a test colloid. The addition of purified fibronectin to plasma obtained from starved rats restored *in vitro* Kupffer cell phagocytic activity to normal. When intravenous fibronectin therapy was administered before the measurement of RE function, the blood clearance and hepatic uptake of the test particle was improved. Dillon *et al.* concluded that the ability to reverse RE depression with purified fibronectin supports the hypothesis that failure of opsonization during starvation is mainly due to fibronectin deficiency. In another study[13] rats starved for 3 days or subjected to haemorrhagic shock had reduced plasma fibronectin concentrations. These animals were also shown to have a reduced fibronectin synthesis, as measured by the reduced incorporation of intravenous ^{14}C-valine into fibronectin and a more rapid clearance of circulating ^{125}I-fibronectin. Therefore, changes in fibronectin metabolism during starvation or haemorrhagic shock may be responsible for the impairment of host defence mechanisms in these conditions.

Animal models which are used to study the RE system differ from man in their plasma fibronectin response to sepsis. Sepsis in man appears to be a major cause of a reduction in the concentration of circulating fibronectin[14]. However, we and others have previously reported that in animals there is a biphasic response to sepsis, with an initial, transient reduction followed by an increase in plasma fibronectin concentration above preoperative levels[9,15–18]. Grossman *et al.*[17] measured plasma fibronectin in rats with intra-abdominal abscesses and rabbits subjected to the generalized Schwartzman reaction

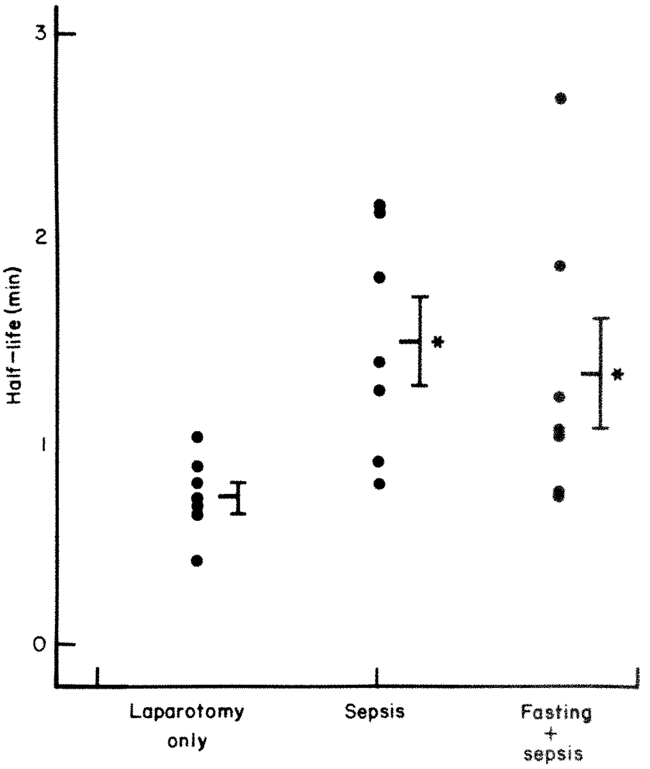

Figure 4 *Blood clearance kinetics of 99^m technetium tin colloid for the laparotomy only, sepsis, and fasting and sepsis groups.* *$P<0{\cdot}02$, *compared with laparotomy only group*

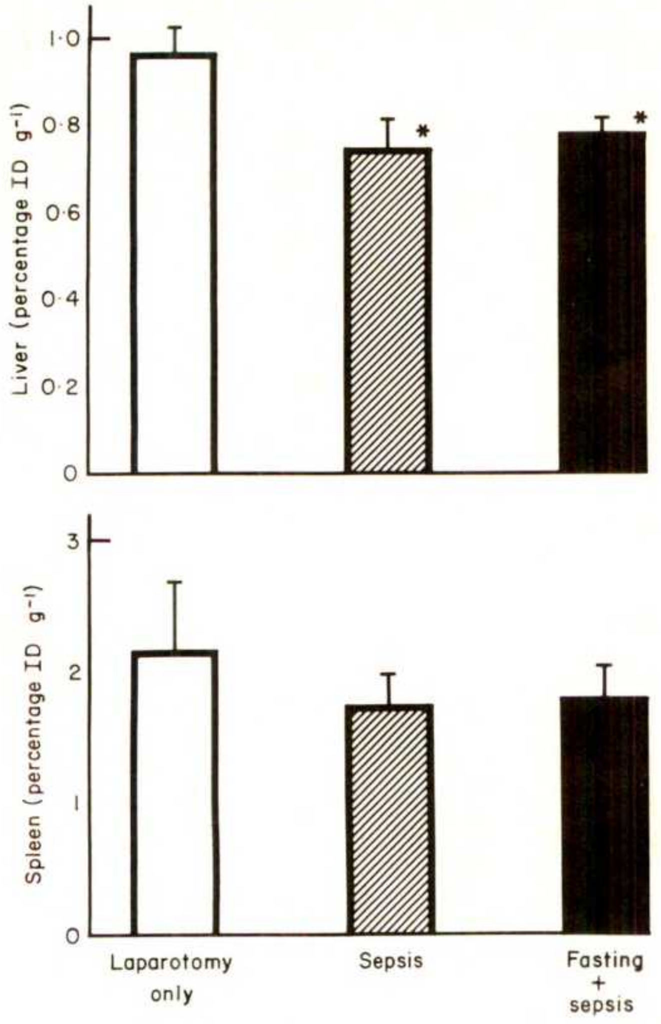

Figure 5 *Distribution of 99^m technetium tin colloid (as percentage injected dose g^{-1} of tissue) to the liver and spleen for the laparotomy only, sepsis, and fasting and sepsis groups.* $^*P<0{\cdot}05$, *Mann–Whitney* U *test, compared with laparotomy only group*

(spaced doses of endotoxin) and found that there was a significant increase rather than a decrease in plasma fibronectin concentrations at times when sepsis and disseminated intravascular coagulation were manifest. Raised concentrations have also been reported after trauma[19] and intraperitoneal inflammation[20]. In both of these studies there was enhanced clearance of blood-borne gelatin-coated lipid test particles, but in the former this was measured after fibronectin had returned to normal. In other studies, rats given intravenous *Escherichia coli* endotoxin[21] or with *E. coli* bacteraemia[22] showed impaired RE phagocytic function, but either no change or an increase in the bioassayable concentration of fibronectin. One study has shown that the hepatic uptake of gelatinized lipid particles was stimulated at the time of elevated serum fibronectin concentrations in rats given intraperitoneal *Staphylococcus aureus* or *E. coli*[23].

Three studies[9,10,23] have measured RE function at times when plasma fibronectin was raised during intraperitoneal sepsis and in two[9,10], as in the present study, there was impaired clearance of test particles with reduction in their uptake by hepatic Kupffer cells. However, in the third[23], the RE clearance of gelatinized lipid particles was increased, suggesting stimulation of Kupffer cell phagocytic activity. Aukburg and Kaplan[9] showed that RE clearance function failed to improve in fibronectin-treated rats after caecal ligation and puncture followed by caecectomy. Restoration of plasma fibronectin to normal or supranormal levels in the post-injury period has been associated with recovery in patients, whereas persistently low levels indicate a poor prognosis[24]. In septic animals, elevation of plasma fibronectin level seems to be associated with RE depression and reduction in fibronectin level may, therefore, precede recovery of RE function. On the other hand, Grossman *et al.*[17] found that fibronectin concentrations remained elevated in non-surviving animals until death.

In the present study, when animals were fasted for 48 h before the induction of sepsis, no significant increase in concentration of fibronectin occurred. By contrast, Velky *et al.*[18] showed that, although there was a significant depression of plasma fibronectin and of total protein level in rats fasted for 7 days, fasting did not interfere with the rapid 24–48 h plasma fibronectin elevation in response to sepsis induced by caecal ligation and puncture. The present study shows that fasting, even for a relatively short time, results in a reduction in plasma fibronectin concentration and that it can prevent the normal fibronectin response to sepsis in a rabbit model. This suggests that acute starvation may be an important factor contributing to the sustained decrease in fibronectin concentrations observed in septic, surgical patients. The relationship between RE phagocytic function and circulating fibronectin values in sepsis is unclear. Changes in fibronectin concentrations in man have been shown to correlate with RE phagocytic function but this is not so for animal models of sepsis. Although fibronectin-depleted animals have an increased mortality from

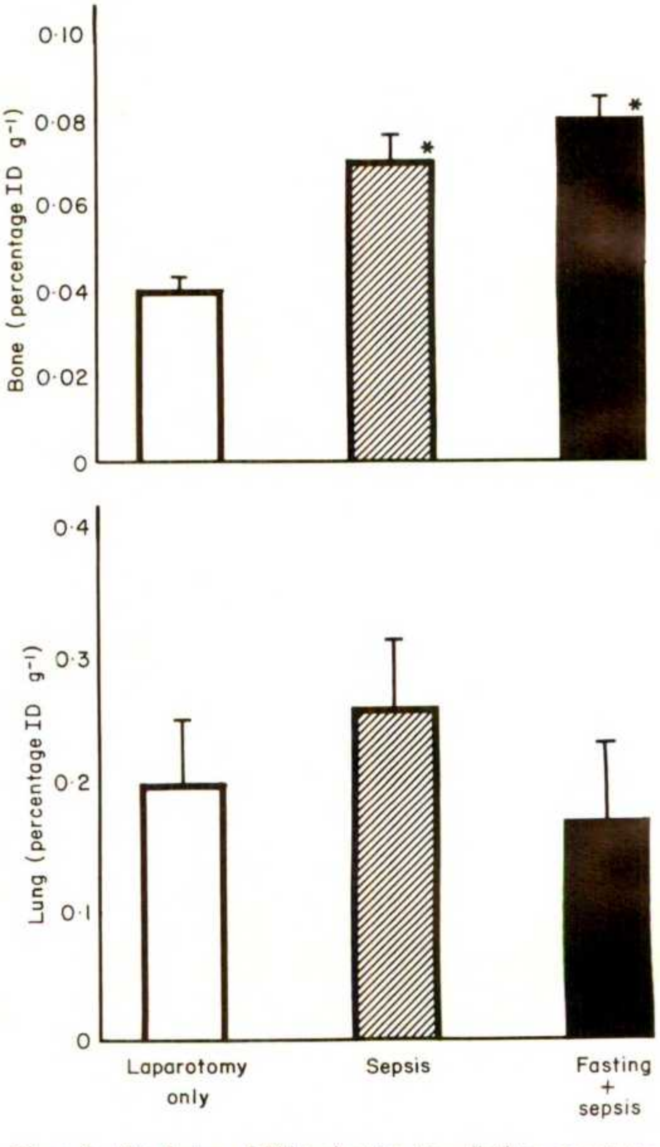

Figure 6 *Distribution of 99^m technetium tin colloid (as percentage injected dose g^{-1} of tissue) to the bone and lungs for the laparotomy only, sepsis, and fasting and sepsis groups.* $^*P<0{\cdot}005$, *Mann–Whitney* U *test, compared with laparotomy only group*

infection[16], in the present study the fasting and sepsis and the sepsis groups showed a similar degree of RE functional impairment despite differences in plasma fibronectin concentrations. The apparent dissociation between plasma fibronectin concentration and RE phagocytic function during sepsis in animal models casts doubt on current concepts of the importance of fibronectin to RE function.

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Monocyte HLA-DR antigen expression characterizes clinical outcome in the trauma patient

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Immunological assessment is important to characterize the host defence response of trauma patients as infection is the most common cause of severe morbidity and late death. Sixty trauma patients were followed serially and divided into three groups: those with an uneventful recovery (n = *17*)*, those with recovery after major sepsis* (n = *27*) *and those who died* (n = *16*)*. The ability of peripheral blood monocytes to express the antigen HLA-DR was measured and compared to the results from 77 asymptomatic volunteers. After initial injury, there was a significant reduction from normal in the three trauma groups. It took one week for HLA-DR antigen expression to return to the normal range in the first group, three weeks in the second group, and in the third group it never returned to normal. Monocyte HLA-DR antigen expression, after incubation with lipopolysaccharide, distinguished those patients who survived from those who died. There was no difference in HLA-DR antigen expression between a high transfusion group of 31 patients who received 10 or more units of blood and a low transfusion group of 29 patients who received less than 10 units. The ability of monocytes to express HLA-DR antigen correlated directly with the clinical course in these patients and its measurement identified a group of patients at high risk of infection and death following trauma.*

Keywords: Trauma, infection, monocyte, HLA-DR, immunosuppression

Infection continues to be a problem in the surgical patient despite advances in operative technique and perioperative management[1]. The victim who has sustained major trauma or burn injury is at especially high risk of developing subsequent infection because of initial bacterial contamination, shock and a suppressed immune response[2–4]. Virtually all aspects of the immune response have been reported to be depressed following injury and surgery, including macrophage, lymphocyte and neutrophil function, delayed hypersensitivity skin test response, immunoglobulin production and serum opsonic capacity[5–12]. Few studies, however, have correlated these tests of immune function with eventual outcome in terms of mortality and infectious complications. We have found two measurements to be of particular importance in the prediction of outcome: the ability of peripheral blood monocytes to express the cell surface antigen HLA-DR[13], and the ability of serum to opsonize bacteria for phagocytosis by normal neutrophils[14].

Most investigators agree that the initial event in the generation of the specific immune response is uptake and degradation of foreign antigens by macrophages[15,16]. The major histocompatibility (MHC) class II antigens (HLA-DR in humans) appear to be critical to the T cell response that follows because T helper cells will only recognize and respond to foreign antigens that are presented on the macrophage cell surface in proximity to HLA-DR antigen molecules[17]. The ultimate response is T cell activation with subsequent B cell immunoglobulin production and enhanced phagocytosis of opsonized bacteria. HLA-DR bearing monocytes, therefore, play a central role in the generation of the immune cascade and we report their behaviour in relation to clinical outcome in 60 severely injured patients.

Patients and methods

The study group consisted of 60 consecutive patients admitted to the trauma service at University Hospital in Louisville, Kentucky, USA. All had sustained major trauma or burns and had an injury severity score (ISS) of at least 20. Patients with a previous medical history of myocardial infarction, organ failure, neoplastic disease or current immunosuppressive therapy (steroids or cytotoxic drugs) were excluded. Patients transferred from other centres after initial stabilization were accepted, but those transferred after prolonged care were not. Informed consent was obtained from the patient or relatives in all cases.

The ISS and $\%LD_{50}$ values were calculated for each patient using the abbreviated injury scale (AIS) table[18]. The coded value for each of the six body compartments was squared and the sum of the three largest squared numbers was used as the ISS. The $\%LD_{50}$ value is simply the ISS corrected for age; this was derived by dividing the ISS by one of three factors dependent on the age of the patient[19].

Venous blood was taken within 24 h of admission and then serially throughout the patient's stay in hospital as well as in the follow-up trauma clinic. Expression of HLA-DR antigen on peripheral blood monocytes was identified by a previously described dual monoclonal antibody staining technique[14]. Briefly, $40\,\mu l$ aliquots of buffy coat cells prepared from acid–citrate dextrose anticoagulated blood were stained for 20 min with both fluorescent labelled antiMO2 (Coulter Immunology, Hialeah, Florida, USA) and antiHLA-DR (Becton-Dickinson, Sunnyvale, California, USA) monoclonal antibodies in the presence of 0.1 per cent sodium azide. Erythrocytes were removed by hypotonic lysis and the samples were preserved with 1 per cent paraformaldehyde. Sample analysis was performed on a cytofluorograph IIS flow cytometer (Ortho Diagnostics, Westwood, California, USA) with simultaneous two-colour discretion to detect both fluorescent-labelled antibodies. By this method, only cells that stained with the monocyte specific antibody, MO2, and HLA-DR were analysed for the coexpression of HLA-DR antigen. In addition, paired aliquots of blood were incubated with lipopolysaccharide (LPS) ($10\,\mu g/ml$) for 2 h and were then analysed as described. At least 100 monocytes were analysed in each sample and complete white blood cell count and differential cell counts were carried out to calculate absolute monocyte numbers per millilitre of blood. Studies of 77 asymptomatic volunteer subjects demonstrated highly reproducible results, showing no effect of age, sex race, time of day, week or year on the levels of HLA-DR expressio in any given subject. There was, however, a linear decrease to n detectable level of antigen at 19 days of storage at 4°C, and so al samples were stained within 4 h of venepuncture.

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The total number of units of blood transfused during initial resuscitation (within 48 h of injury) was also recorded. The majority of patients received units of packed red blood cells, each of a volume of 200–250 ml. A few transfusions were given as whole blood units of 500 ml each. The 60 patients were divided into a high transfusion group of 31 patients who received 10 or more units of packed red blood cells or whole blood and a low transfusion group of 29 patients who received less than 10 units. Serial samples from four units of packed red blood cells were withdrawn over a 19 day period for monocyte HLA-DR antigen measurement, with and without LPS incubation, to assess temporal changes in the expression of this antigen.

Results are expressed both in terms of the percentage of total MO2 staining monocytes that expressed HLA-DR and as mean fluorescence intensity of the gated MO2 positive cells; this is an expression of the density of HLA-DR expression. These results are compared with those derived from the control population of 77 uninjured volunteers, free of medical illness and ranging in age from 20 to 91 years. Results are expressed as mean (s.e.m.) values. The percentage data were transformed to the arcsines of their square roots to produce a nearly normal distribution before statistical analysis. When three or more groups were compared over the same time period, a 2-tailed, 1-way analysis of variance was performed. Student's t tests for unpaired samples were then used to compare results and determine statistical significance. Differences were considered significant at $P<0.05$.

Results

Patients were divided into three clinical outcome groups: a good outcome group of patients who did not develop major sepsis ($n=17$), a group who survived major sepsis ($n=27$) and a group of patients who died ($n=16$). Of the 16 patients in the third group 14 died of overwhelming infection with multiple system organ failure (MSOF), while the other two died from progressive hypoxia within 4 days of admission. Major sepsis was strictly defined as bacteraemia not associated with central lines, pneumonia, major wound or soft tissue infection, intra-abdominal abscess or other body cavity abscess, and the need for reoperation for sepsis, all of which prolonged hospital stay. The demographic make-up of each group, including ISS and %LD$_{50}$, is listed in *Table 1*.

Relative monocytosis was seen in all patients, usually beginning by the third day after injury, becoming maximal on the 11th day after hospital admission, and returning slowly to normal over several weeks (*Figure 1*). The normal range, obtained from our cohort of 77 asymptomatic volunteers, was about 100–600 monocytes/ml on peripheral smear. Interestingly, monocytosis was least marked in the group of patients who died, although differences did not reach statistical significance (*Figure 1*).

In the control population 85 (1·7) per cent of monocytes expressed HLA-DR and the mean fluorescence intensity was 162 (3·8) per cent. We arbitrarily defined the normal range as mean (1·5) standard deviations (range 70–100 per cent), since 100 per cent is the highest possible value and only six of the control population had values below 70 per cent. The percentages of monocytes that expressed HLA-DR in the three clinical outcome groups are shown in *Figure 2*. All three groups had a depression below the normal range within 24 h of hospital admission. The two groups of patients who survived showed an eventual return of their mean values to within the normal range, but at differing times from initial injury. In the uneventful recovery group, the mean HLA-DR antigen expression returned to 70 per cent by 1 week and 85 per cent by 4 weeks. In the major sepsis group, mean HLA-DR antigen expression returned to 70 per cent after 3 weeks, but never reached 85 per cent during the period studied. Mean HLA-DR antigen expression steadily declined in the third group until the time of death.

Table 1 *Demographic make-up of the clinical outcome groups*

	Uneventful recovery	Major infection	Death
Age (years)	33 (17–62)	33 (18–56)	52 (19–91)
Sex (male:female)	15:2	20:7	11:5
ISS*	33 (25–50)	29 (20–50)	42 (20–50)
%LD$_{50}$†	85 (63–141)	85 (50–125)	125 (80–250)
Penetrating injury	5	13	2
Blunt injury	11	9	6
Burns	1	5	8

* ISS, injury severity score; † LD$_{50}$, ISS corrected for age; figures in brackets denote range of values

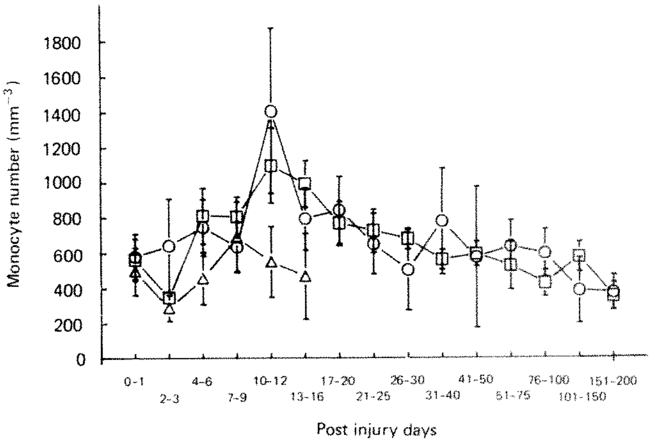

Figure 1 *Monocyte counts following severe injury: ○, uneventful recovery group; □, major sepsis group; △, group of patients who died. Error bars refer to the standard error of the mean*

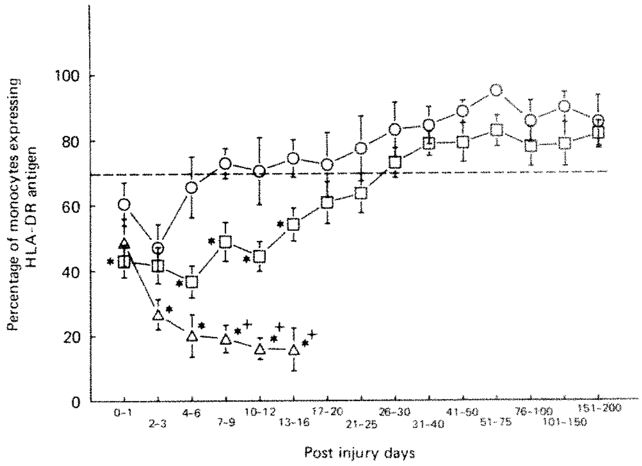

Figure 2 *Percentages of monocytes that expressed HLA-DR antigen after severe injury: ○, uneventful recovery group; □, major sepsis group; △, group of patients who died. Error bars refer to the standard error of the mean. * Statistically significant difference from uneventful recovery group; $^+$ statistically significant difference from major sepsis group*

A similar pattern of results was seen when the mean fluorescence intensity (HLA-DR density) data were analysed (*Figure 3*). Depressed values returned to normal in the surviving groups but not in the group of patients who died. *Figure 4* shows a plot of HLA-DR antigen expression following 2 h incubation with LPS over time in the three clinical outcome groups. In both groups of surviving patients, the percentages of monocytes expressing MO2-DR were always within the normal range (> 70 per cent). Patients who were destined to die exhibited monocyte HLA-DR antigen expression after LPS incubation below the normal range from day 1 until the time of death. Statistical significance was reached between the surviving groups and the dead group as shown on *Figure 4*.

There was no significant difference in HLA-DR antigen expression between the 31 patients in the high transfusion group and the 29 patients in the low transfusion group, although the high transfusion group did have slightly higher values over the first 2 weeks after admission to hospital. To study the effect of

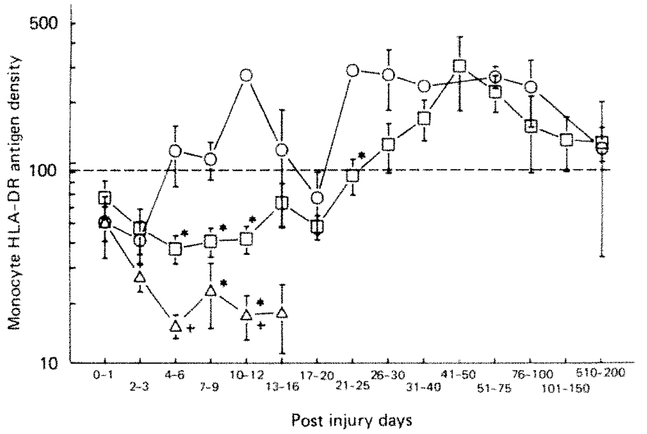

Figure 3 *Density of monocyte HLA-DR antigen after severe injury: ○, uneventful recovery group; □, major sepsis group, △, group of patients who died. Error bars refer to the standard error of the mean. * Statistically significant difference from uneventful recovery group; ⁺ statistically significant difference from major sepsis group*

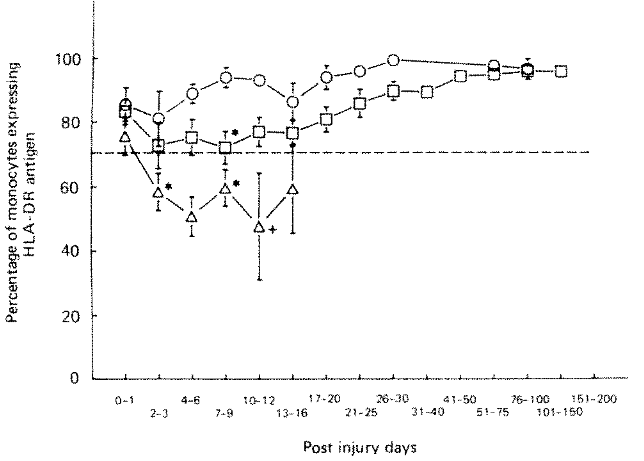

Figure 4 *Percentage of monocytes that expressed HLA-DR antigen after incubation with lipopolysaccharide: ○, uneventful recovery group; □, major sepsis group; △, group of patients who died. Error bars refer to the standard error of the mean. * Statistically significant difference from uneventful recovery group; ⁺ statistically significant difference from major sepsis group*

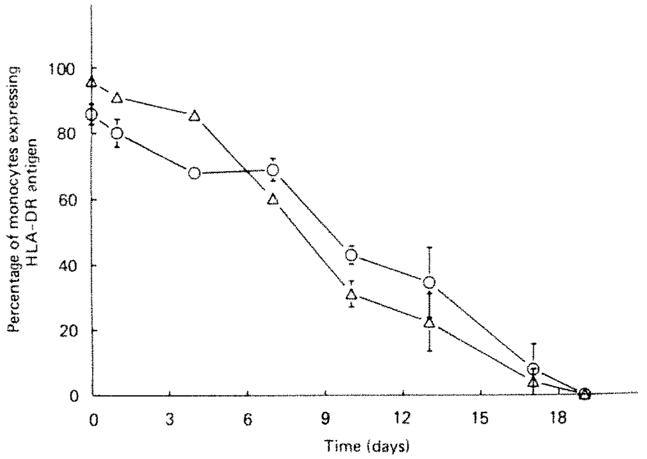

Figure 5 *Serial analysis of HLA-DR antigen expression of monocytes from stored blood: ○, baseline results; △, results after lipopolysaccharide incubation. Error bars refer to the standard error of the mean*

time on HLA-DR antigen expression, 4 units of freshly packed cells were sampled 8 times over a period of 19 days (*Figure 5*). There was a steady, linear decline in HLA-DR antigen expression over the period until none was detected on day 19. In contrast to the surviving patients, LPS incubation did not result in appreciably higher values at any time throughout the experiment and values were actually less after day 6.

Discussion

Trauma induced deaths can be divided into those that occur early, usually due to ongoing haemorrhage or cerebral injury, and those that occur late, which are almost always associated with infection[2,3]. We have found that the occurrence of sepsis is not entirely related to the severity of injury (as measured by ISS) or predicted by clinical assessment of the amount of bacterial contamination at the time of injury[13]. A variety of immunological measurements has been made in injured patients and an early depression of the overall immune response has been well documented[5–12]. The central role of the macrophage has become clearer through Faist's research, which has shown increased prostaglandin-E2 production, and reduced IL2 and interferon-gamma production, presumably as a result of inhibitory macrophages[7]. Our results show a relative monocytosis, confirming previous work[7,13], but an overall reduction in monocytes that express surface HLA-DR. The smallest increase in peripheral monocytes occurred in the patients who died; they also had the lowest HLA-DR expression. This indicates that an increase in immature monocytes was not responsible for reduced HLA-DR expression. Furthermore, monocytes from surviving patients were able to express this antigen after incubation with LPS signifying a down regulation in HLA-DR expression after injury.

Although we have shown that MO2-positive monocyte HLA-DR expression measurement, performed within 24 h of admission after injury, was reduced in virtually all patients, serial measurements gave more information. An upward trend in HLA-DR expression was highly predictive of recovery, whether or not infection supervened. Conversely, the patients who died showed a constant downward trend despite LPS incubation. Monocyte HLA-DR expression together with injury severity, age and bacterial contamination have been incorporated into an outcome predictive score which reliably predicts uneventful recovery from major infection or death in trauma patients[20].

The highest rate of infection was in burn patients since those who qualified for the study had at least 40 per cent second and third degree burns. In addition, the age and ISS of the patients who died were significantly greater than those of the patients who survived, although there was little difference between the group with major infection and those who recovered without sepsis. The major infection group was composed of slightly more patients with penetrating injury than the group without sepsis. This may suggest a greater bacterial contamination through colonic injury in the former group.

Transfusion had no significant effect on HLA-DR antigen expression despite a linear decrease in the ability of monocytes from stored blood to express HLA-DR. The blood given to our patients was about nine days old on average and so values of HLA-DR antigen expression in this study reflect those of the patients' own monocytes rather than those of transfused monocytes. Controversy exists concerning whether massive transfusion predisposes to infection following trauma[21]. We did not find an increased rate of major infection in the group that had more than 10 units of blood compared to the group that had less than 10 units.

The use of the monoclonal antibody antiMO2 allows consistent identification of a similar population of monocytes since the MO2 antigen is not expressed on B, T or null lymphocytes, or neutrophils[22]. The test is simple to perform and requires only 4 h in centres equipped with flow cytometry. Measurement of monocyte HLA-DR antigen expression is a useful adjunct to overall clinical impression and helps to identify at an early stage those trauma patients who are at especially high risk of infection and death. This may permit earlier therapeutic intervention with new measures as they become available.

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Electrically stimulated sartorius neosphincter: canine model of activation and skeletal muscle transformation

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The sartorius muscle was transposed into the abdominal cavity of six dogs, passed around a Thiry–Vella loop and sutured to itself to form a neosphincter. The muscle was activated by electrical stimulation and on contraction the neosphincter stopped or reduced the flow of saline through the Thiry–Vella loop in all animals until the onset of muscle fatigue. Continuous low frequency stimulation was used to transform the skeletal muscle, and when studied after a mean of 8 weeks of stimulation (range 6–11 weeks) the neosphincter stopped the flow for a significantly longer period of time (P = 0·027). Associated with the improved neosphincter function was a significant decrease in the fusion frequency (P = 0·003) and prolongation of the stimulus–peak tension time as assessed by a strain gauge sutured to the neosphincter muscle (P = 0·002). The changes in the contraction properties of the skeletal muscle suggest that continuous low frequency stimulation transformed the muscle fibres from type 2 to type 1, resulting in improved fatigue resistance and potential for continuous sphincter activity.

Keywords: Skeletal muscle neosphincter, electrical stimulation, fibre type transformation, improved fatigue resistance

The gracilis sling procedure was described by Pickrell *et al.* in 1951 as a treatment for selected cases of faecal incontinence[1]. Reports of its use in the literature are sparse, often uncritical, and usually only describe small numbers of patients. The results of the operation are inconsistent and apart from a few enthusiasts[2,3] it has never gained general acceptance and is therefore not widely used.

The operation is likely to fail because the innervation of the gracilis is inappropriate for sphincter action and this cannot be improved. The gracilis is a muscle of mixed type, containing mainly type 2, fast-twitch, fatiguable fibres. It is therefore unsuitable to maintain the continuous contraction necessary for sphincter function. Some surgeons argue, however, that the gracilis sling is totally adynamic and merely acts as a type of Thirsch wire.

Electrical stimulation by implanted stimulators is routinely used in medical practice for pacing the heart in patients with cardiac arrhythmias[4] and in the treatment of intractable pain[5]. Electrical stimulation of the gracilis muscle might give the contraction and control needed for sphincter function. Additionally chronic low frequency stimulation could transform the muscle to a slow-twitch, fatigue-resistant type 1 muscle[6], able to sustain contraction for a prolonged period of time, and therefore make it more suitable for sphincter function.

The aim of this study was to develop a canine model to test the hypothesis that electrically stimulated striated muscle could function as a neosphincter, with the properties of slow twitch, tetanic fusion at a low frequency of stimulation and fatigue resistance.

Methods

Animals and surgical procedure

Six adult beagles (two male, four female; mean weight 13·6 kg, range 9·6–16·0 kg) were used. The canine gracilis muscle[7], unlike the human, is a short and broad muscle unsuitable for use as a neosphincter. The superior belly of the canine sartorius muscle is similar to the human gracilis muscle. It is long, thin and strap-like with a proximal innervation and blood supply[7], and was therefore chosen to form the neosphincter in this study.

Anaesthesia was induced with methohexitone sodium 15 mg/kg intravenously. An 8 mm diameter endotracheal tube (Portex Ltd, Hythe, UK) was inserted and anaesthesia was maintained during spontaneous respiration with a mixture of halothane, nitrous oxide and oxygen. Antibiotic prophylaxis (cefuroxime 750 mg and metronidazole 500 mg) was given intravenously on induction of anaesthesia because of the nature of the surgery and the implantation of the stimulators.

A midline laparotomy was performed and a 20 cm Thiry–Vella loop was formed from the midileum and two flush ileostomies were raised in the right flank. Intestinal continuity was restored by an end-to-end anastomosis.

An incision was made over the medial aspect of the left hind limb from the inguinal ligament to the knee. The superior belly of the sartorius muscle was identified and dissected free from the surrounding structures; it was detached distally and the dissection continued proximally until the neurovascular pedicle was identified. It was carefully preserved and the muscle was maximally mobilized and then passed into the abdominal cavity through a femoral canal greatly enlarged by division of the inguinal ligament. The muscle was then passed around the Thiry–Vella loop and sutured to itself so as to completely encircle the loop and form a neosphincter.

The electrodes used to stimulate the muscle nerve were the bared ends of fine insulated wires (Temporary Cardiac Pacing Wire, F EP 13, Ethicon, Edinburgh, UK). The other ends of the wire were connected to a multipin electrical socket contained within a stainless steel cannula which traversed the abdominal wall through a stab incision in the left flank. The position of the electrodes was determined by measuring the threshold of muscle twitch to electrical stimulation from an external stimulator (Grass SD9®, Grass Medical Instruments, Quincy, Massachusetts, USA) connected via the abdominal cannula. Once the optimal position with the lowest threshold for muscle contraction was determined the electrodes were sutured to the muscle, care being taken to avoid damaging the nerve and blood supply. Five animals also had a second pair of stimulating electrodes sutured close to the muscle nerve. In three dogs these were connected to a Medtronic 3522® receiver (Medtronic Neuro, Minneapolis, Minnesota, USA) activated by transcutaneous induction by an antenna and external receiver. In two dogs these were connected to an externally programmable totally implantable Itrel 7420® stimulator (Medtronic Neuro). The receiver or

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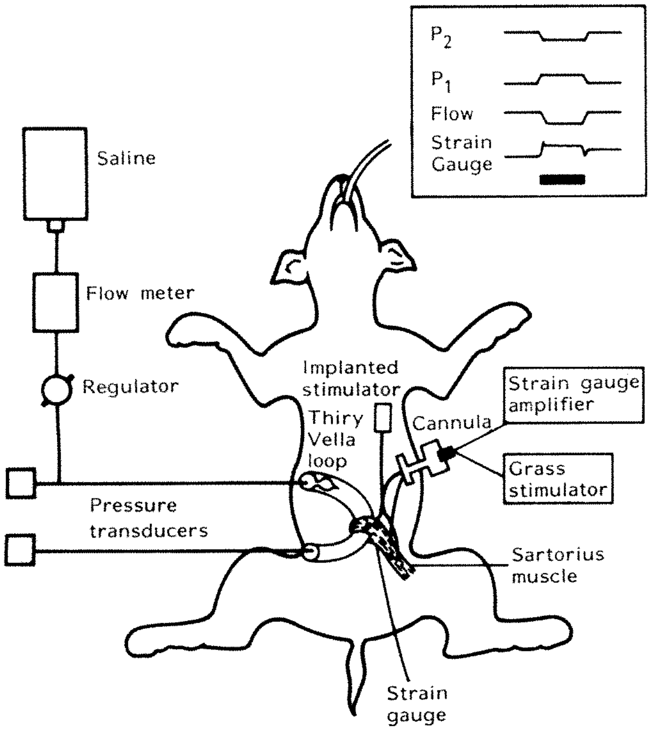

Figure 1 *Assessment of canine sartorius neosphincter function. The sphincter encircling the Thiry–Vella loop was activated electrically by the external stimulator. The flow of saline into the loop, the pressures proximal and distal to the sphincter and the sphincter contraction assessed by a strain gauge were displayed on a chart recorder. The solid bar shows the period of stimulation*

stimulator was implanted subcutaneously over the left chest wall. Four animals had a sensitive strain gauge[8] sutured to the portion of the sartorius which formed the neosphincter. The strain gauge leads were connected to an external amplifier via the abdominal wall cannula. The sphincter was tested peroperatively to ascertain that the electrodes were situated appropriately, resulting in an adequate sphincter-like contraction on stimulation with a single twitch detectable by the strain gauge.

Continuous low frequency stimulation (CLFS)

The neosphincter was assessed physiologically 2 weeks after surgery as described below. Following this CLFS (2–4 pulses/s; pulse duration 0·2 ms) was commenced in the five dogs with implanted stimulators or receivers. The dogs with the Medtronic 3522® receivers carried the stimulator control unit in a special jacket which also served to keep the antenna in position. The neosphincter was reassessed physiologically after a mean of 8 weeks of CLFS (range 6–11 weeks).

Assessment of neosphincter function (Figure 1)

The function of the neosphincter was assessed by its ability to reduce the flow of saline through the Thiry–Vella loop when stimulated to a tetanic contraction by the external Grass stimulator. Initial attempts to study sphincter function with the animals awake on a stand were thwarted by respiratory and movement artefacts, and consequently intubated general anaesthesia with spontaneous respiration as described above was used for all sphincter studies.

The two stomas of the Thiry–Vella loop were intubated with latex 14 F Foley catheters (Bard Limited, Sunderland, UK) and the balloons were inflated to achieve a watertight seal. The loop was perfused with saline by gravity-induced flow; the maximum perfusion pressure possible was 100 cmH$_2$O. The flow rate was adjusted by a regulator valve with the sphincter relaxed until it reached the maximum registrable on the linear range of a modified drip counter (IVAC 231® controller and IVAC 170® drop sensor, IVAC Corporation, San Diego, California, USA) used as a flow meter. The pressures proximal and distal to the sphincter were measured by two pressure transducers (Gould-Statham P50®, Gould Electronics, Ilford, UK, and Neurolog PDCR 75 S/N 1873®, Digitimer Ltd., Welwyn Garden City, UK). The strain gauge was connected to a purpose built external amplifier via the abdominal wall cannula. The signals from the pressure transducers, the flow meter and the strain gauge were recorded on a four-channel ink jet recorder (Gould Brush 2400®, Gould Electronics).

Fusion frequency

The threshold for muscle contraction detected by the strain gauge and pressure signals was determined with a stimulus pulse duration of 0·2 ms and a frequency of 30 pulses/s. With a suprathreshold voltage the effect of varying the stimulus frequency was assessed. The minimum stimulus frequency which resulted in a smooth fused plateau in the strain gauge and pressure signals, implying a tetanic contraction, was defined as the fusion frequency.

Stimulus–peak tension time

The signal from the strain gauge was displayed on the screen of a digital storage oscilloscope (Gould 'advanced' OS 400®, Gould Electronics). The neosphincter was stimulated at 1 pulse/s and the sweep of the oscilloscope was triggered by a prepulse from the Grass stimulator 200 ms before the actual stimulus. The strain gauge signal showed the stimulus artefact and the time course of the resulting twitch. A permanent record was obtained by taking a photograph of the stored image from the oscilloscope screen with a Polaroid® camera (Kodak, UK, CR9 Land camera) and the time from the stimulus to the development of peak tension was measured and defined as the stimulus–peak tension time.

Duration of sphincter competence

The neosphincter was activated by a suprathreshold stimulus at the fusion frequency with a stimulus pulse duration of 0·2 ms. The resulting flow, strain gauge and pressure changes were recorded by the chart recorder (*Figure 1*). The stimulation was continued until the onset of presumed muscle fatigue and the resumption of flow, when the stimulation was terminated. The time from the commencement of stimulation to the onset of muscle fatigue and the return of flow through the Thiry–Vella loop was defined as the sphincter competence duration.

Resistance of non-activated neosphincter

The flow and pressure across the non-activated neosphincter were measured before and after the period of CLFS. The flow/pressure ratio was calculated as an index of resistance in each study.

Histology

A standard series of enzyme histochemical methods[9] was used to study muscle fibre morphology and fibre type in muscle biopsy specimens taken from the sartorius muscle when the animals were killed under terminal anaesthesia. Muscle specimens were obtained from the sartorius muscle which formed the neosphincter; samples from a homologous site on the contralateral sartorius served as controls. The muscle specimens were quenched in isopentane cooled with liquid nitrogen and sectioned in the transverse plane in a cryostat.

Analysis of results

Results are presented as mean (s.e.m.). Statistical analysis was by Student's t test for paired data (two-tailed), and a value of $P<0·05$ was considered to be significant.

Ethical approval

The study was licensed under the new regulations of the Animals (Scientific Procedures) Act 1986.

Results

The animals tolerated the surgical procedures, sphincter assessments and general anaesthesia well without any serious complications. The sphincter could be felt and seen contracting when CLFS was in progress. The dogs did not appear to be aware of the muscle stimulation and were able to lead a normal kennel life throughout the study.

Figure 2 shows the Thiry–Vella loop of one dog outlined by radiopaque contrast medium on a radiograph. The site of the sphincter can clearly be seen and when the sphincter was activated it obliterated the lumen over a length of approximately 1·5 cm.

The sphincter was able to stop the flow of saline through the loop completely for a varying period when activated by a tetanic stimulation before the period of CLFS in four of the six animals (*Figure 3*). In two dogs the flow did not cease completely, but there was a marked reduction.

Activation of the neosphincter with tetanic stimulation caused a sudden displacement of the strain gauge signal

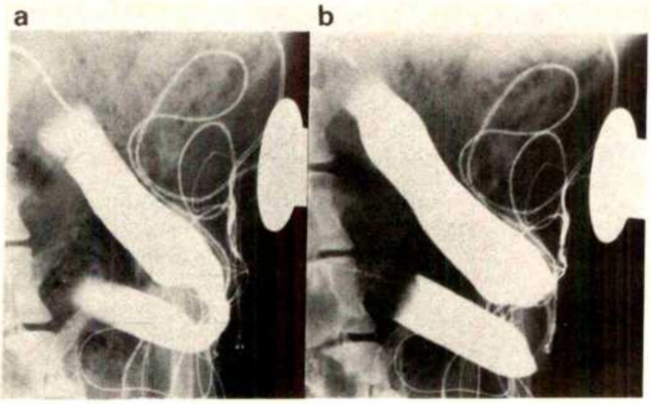

Figure 2 *Radiograph of Thiry–Vella loop containing radio-opaque contrast medium. The site of the neosphincter can be seen,* **a**, *with the sphincter relaxed. In* **b** *the sphincter was activated and obliterated the lumen over a length of 1·5 cm. The abdominal wall cannula, stimulating electrodes and strain gauge with its wires can also be seen*

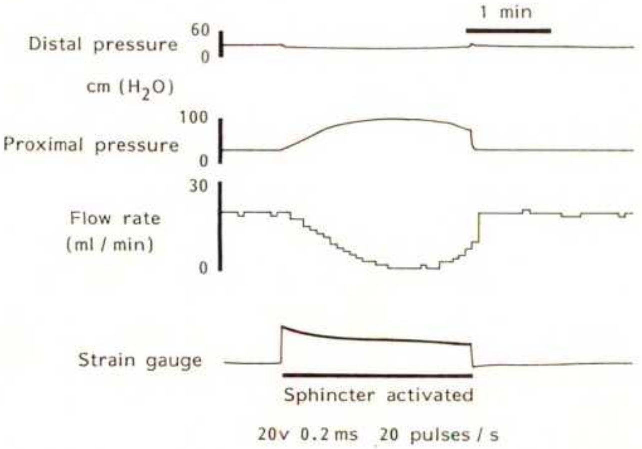

Figure 3 *Record of canine sartorius neosphincter assessment. The upper two traces show the pressures distal and proximal to the neosphincter. The third trace shows the flow rate into the Thiry–Vella loop proximal to the neosphincter and the lowest trace shows the neosphincter strain gauge signal*

(*Figure 3*). The flow into the Thiry–Vella loop gradually decreased and eventually stopped, accompanied by a gradual increase in the pressure proximal to the sphincter, and a sudden small decrease in the pressure distal to the sphincter. After an interval the muscle began to fatigue so that the flow gradually returned and the pressure proximal to the sphincter again fell. When the stimulation ceased the traces returned to their prestimulation values.

The time course of the flow and pressure changes can be explained by the pressure within the Thiry–Vella loop proximal to the neosphincter initially being low and the major pressure drop being across the regulator valve. The loop proximal to the neosphincter was therefore able to distend with saline as the pressure within it slowly increased. There was a gradual reduction in the flow into the loop and gradual increase in the pressure within it, even though the occlusion of its lumen by the sphincter was immediate.

In one dog the sphincter functioned well at the first laparotomy, but when assessed 2 weeks later there was no response to stimulation. A second laparotomy was performed and the neosphincter muscle was found to have undergone necrosis, presumably ischaemic; the Thiry–Vella loop was dissected free from the muscle and a second neosphincter fashioned from the contralateral sartorius. A fistula developed between the Thiry–Vella loop and the laparotomy wound. The dog remained well and the sphincter completely stopped the flow of saline through the loop and fistula when activated. This animal did not undergo CLFS.

Effect of CLFS on sphincter muscle function

Fusion frequency. The fusion frequency was reduced from 22·2 (2·3) pulses/s before CLFS to 14·4 (2·8) pulses/s after CLFS ($P = 0{\cdot}003$; *Figure 4*).

Stimulus–peak tension time. The time from the stimulus to peak tension increased from 63 (7) ms before CLFS to 187 (11) ms after CLFS ($P = 0{\cdot}002$; *Figure 5*).

Sphincter competence duration. The sphincters were initially completely competent to saline under 100 cmH$_2$O pressure for 1·4 (0·7) min. After CLFS the sphincter competence duration was significantly increased to 5·6 (1·9) min ($P = 0{\cdot}027$; *Figure 6*).

Flow/pressure ratio. The flow/pressure ratio of the non-activated neosphincter before CLFS was 2·3 (0·65). After CLFS the ratio was unchanged (2·4 (1·14); $P = 0{\cdot}74$).

Histology. In the specimens of sartorius muscle taken from the unoperated leg (control specimens) the muscle fibres were of uniform size, shape and staining intensity, with a mosaic distribution of fibre types of nicotinamide adenine dinucleotide hydrogenase (NADH) and adenosine triphosphatase (ATPase) preparations[9] (*Figure 7*). In the neosphincter muscle specimens from each of the animals there were areas of patchy intrafascicular necrosis and regeneration, which in some specimens involved whole fascicles. These areas contained macrophages and small inflammatory cells, and there were often zones of fatty replacement within them. In addition there was a slight increase in endomysial and interfascicular fibrous tissue (*Figure 8*), and muscle fibres of relatively normal size and shape contained central nuclei. These appearances were consistent with ischaemic necrosis and consequent partial regeneration. The histological features of necrosis and regeneration precluded attempts to study fibre type transformation, since the large numbers of immature fibres usually showed intermediate activity in acid preincubation in the ATPase preparations.

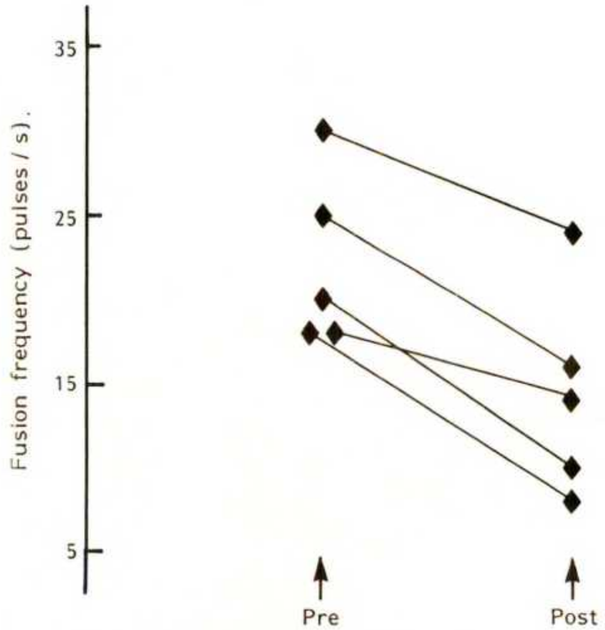

Figure 4 *Fusion frequency before and after chronic low frequency stimulation;* P = *0·003, paired* t *test*

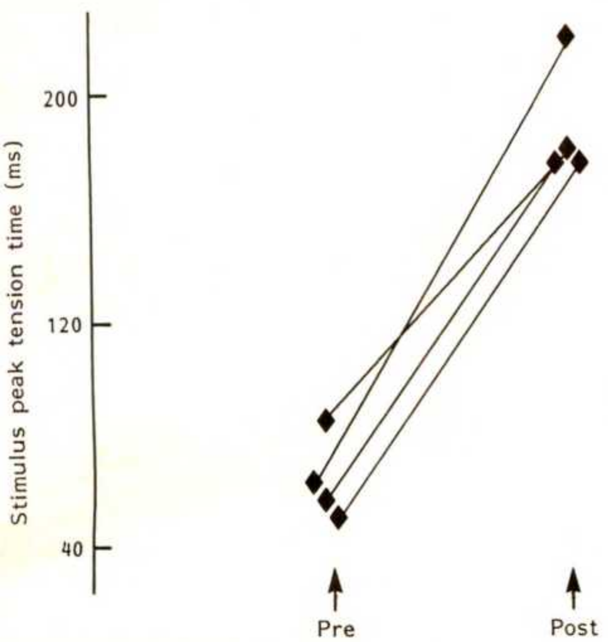

Figure 5 *Stimulus–peak tension time before and after chronic low frequency stimulation;* P = 0·002, *paired* t *test*

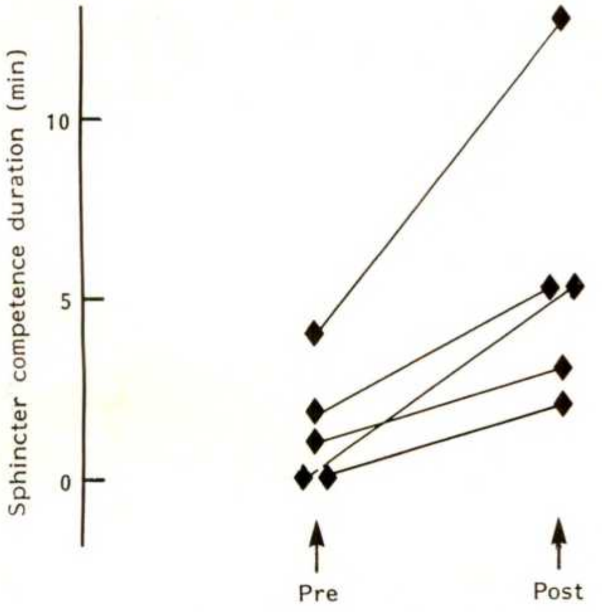

Figure 6 *Sphincter competence duration before and after chronic low frequency stimulation;* P < 0·027, *paired* t *test*

Discussion

These experiments have shown that an electrically stimulated neosphincter formed from limb skeletal muscle is a feasible proposition in an experimental animal model. The model was original in concept and, except for one early technical failure with muscle necrosis and the development of a Thiry–Vella loop cutaneous fistula, was easily performed and reliable in function. When activated the neosphincter was able to prevent or reduce the flow of saline through the Thiry–Vella loop. After a mean of 8 weeks of CLFS the period of time in which the flow could be completely stopped was significantly increased.

The histological changes in the neosphincter muscle consisted mainly of ischaemic necrosis and regeneration, features suggestive of vascular compromise following the mobilization of the muscle. The biopsies were taken from the midportion of the sartorius neosphincter muscle. Macroscopically the distal portion appeared fibrosed, but the good sphincter function showed that the proximal portion, which macroscopically appeared normal, was indeed healthy. The changes in the fusion frequency and the twitch tension curve suggest that functional fibre type transformation from fast-twitch fatiguable type 2 to slow-twitch fatigue-resistant type 1 had occurred in this portion of the sartorius neosphincter. This change is in the direction of that required for adequate sphincter function, for which continuous low activity is required. It is improbable that muscle fibrosis alone was responsible for the prolongation in neosphincter competence duration which occurred with CLFS. Although fibrosis clearly occurred, the index of resistance of the non-activated neosphincter (flow/pressure ratio) was not significantly altered during the study period. Fibrosis would slow down the development of tension, but this effect would not be nearly so great as seen in this study. Furthermore the reduction in fusion frequency cannot be explained on the basis of fibrosis, as other workers have shown that it reverts back to previous values on cessation of CLFS[10]. The histological changes observed in the biopsies were mainly muscle necrosis and regeneration, and the amount of fibrosis was slight. It therefore seems highly likely that muscle transformation had occurred and was responsible for the improvement in neosphincter function.

Mammalian skeletal muscle fibres are classified according

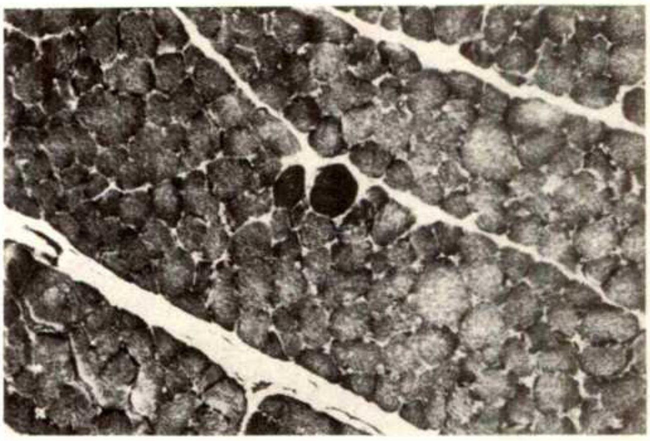

Figure 7 *Control sartorius muscle* × *200, nicotinamide adenine dinucleotide hydrogenase (NADH) stain. The muscle fibres are of a relatively uniform size and shape, and the interfascicular connective tissue is of normal thickness*

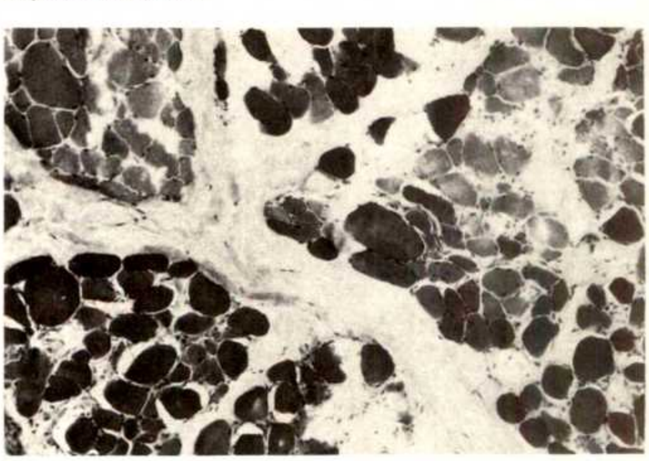

Figure 8 *Sartorius neosphincter after chronic low frequency stimulation* × *200, haematoxylin and eosin stain. There is patchy fibre necrosis and regeneration, with marked variability in fibre size and staining intensity. Fatty infiltration is present and the interfascicular connective tissue is markedly thickened*

to histochemical and physiological criteria[11]. Red, fast-contracting, rapidly fatiguing muscle fibres are classified as type 2, and white, slow-contracting, fatigue-resistant muscle fibres as type 1 according to their reactivity for myosin ATPase in acid and alkaline preincubations[11]. Salmons and Vrobvá initially demonstrated that CLFS could transform type 2 to type 1 skeletal muscle[6]. In a series of animal experiments it has subsequently been shown that complete transformation of fibre type occurs according to physiological, biochemical and morphological criteria of muscle function[12,13]. Physiologically the overall response of the muscle to CLFS is a reduction in contractile speed, a higher twitch/tetanus ratio and a lower fusion frequency for tetanic stimulation. The changes occur as a result of alterations in the kinetics of release and uptake of calcium within the muscle fibres[14,15] and a marked reduction in the quantity of T tubule system and sarcoplasmic reticulum[16]. The light and heavy chain myosin isomers change from those characteristic of fast muscle type to those characteristic of slow muscle type[17], and this is observed biochemically as a reduction in Ca^{2+}-activated myosin ATPase and histochemically as transformation from alkali-stable to alkali-labile staining characteristics, e.g. in myosin ATPase preparations[18]. ATP synthesis is switched from anaerobic glycolysis to oxidative pathways, especially from fatty acids[19]. There is an associated increase in capillary density[20] and a marked increase in mitochondrial volume[16]. The altered morphological, enzymatic and biochemical features of the muscle fibres are consistent with the change in their functional characteristics from type 2 to type 1.

The concept of electrical stimulation to improve sphincter muscle function is not new. Various workers have used this modality to treat anal sphincter weakness. Caldwell implanted electrodes directly into the anal sphincter and used an implanted stimulator to treat rectal prolapse and faecal incontinence, and reported good results in several case reports[21,22]. Hopkinson and Lightwood used an anal plug electrode to stimulate the anal sphincter transcutaneously in one patient with a good result[23] and published a further report of nine cases[24]. Glen reported the use of the plug electrode in a series of 30 patients with a mixture of faecal and urinary incontinence[25]. The overall results were described as good. Of nine faecally incontinent patients one was 'cured' and five were 'controlled'. A report by Duthie's group was very critical of the results obtained in their hands by electrical stimulation of the anal sphincter with plug electrodes in faecal incontinence[26]. In the subsequent 15 years there have however been no further reports of these techniques, implying that further experience has largely been disappointing. These techniques probably failed because the end organ, i.e. the anal sphincter in idiopathic faecal incontinence, is denervated[27], and the changes within it are irreversible. However it should be pointed out that the changes in muscle fatigue resistance resulting from chronic low frequency electrical stimulation were unknown at the time the previous studies were carried out, and the stimulus parameters were therefore not tailored to muscle fibre type transformation.

Nevertheless our concept is entirely different to that of previous workers in that we have taken normal type 2 skeletal muscle and attempted to convert it to type 1 muscle to create a neosphincter with fatigue resistance. The concept of electrical transformation of skeletal muscle has recently been introduced into the clinical arena of cardiac augmentation, and this has been highlighted in two recent editorials[28,29]. Clinical use of converted and synchronously paced latissimus dorsi muscle has been reported in two cases where muscle grafts replaced resected myocardium. There was improvement in the ventricular ejection fraction and long term survival of the patients[30,31].

The electrically stimulated canine sartorius neosphincter functions well. Current surgical procedures for faecal incontinence such as postanal repair are only moderately successful[32] and in the long term may be disappointing[33]. Applying the technique of electrostimulation to the human situation brings the potential of greatly improving the results of the gracilis sling procedure and the quality of life of faecally incontinent patients in whom conventional treatment has failed. Baeten and colleagues recently reported the case of a patient who had an initially successful gracilis sling procedure as a child, which in adult life was augmented by the implantation of electrodes into the gracilis muscle at its motor point connected to an implanted stimulator. She was completely continent when the gracilis muscle was activated electrically[34]. We have now developed our animal model into a technique suitable for clinical application and have used this to treat patients with faecal incontinence refractory to conventional surgical procedures, with encouraging initial results[35].

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Effects of an amino acid solution enriched with either branched chain amino acids or ornithine-α-ketoglutarate on the postoperative intracellular amino acid concentration of skeletal muscle

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Patients undergoing elective cholecystectomy provide a highly reproducible model of the effects of trauma on intermediary metabolism. Three parenteral nutrition regimens were given to groups of eight such patients. An isonitrogenous total parenteral nutrition, including a commercially available amino acid solution, an amino acid solution enriched with branched chain amino acids or one supplemented with ornithine-α-ketoglutarate, was given after operation. The intra cellular free amino acid concentrations of skeletal muscle were determined in tissue specimens obtained before operation and on the third postoperative day using a percutaneous needle biopsy technique. The mean(s.e.m.) decrease in the concentrations of free intracellular glutamine on the third postoperative day was less pronounced ($P<0{\cdot}05$) *in the ornithine-α-ketoglutarate group (18·8(7·5) per cent) than in the control group (39·4(5·1) per cent) or the branched chain amino acid group (45·3(6·1) per cent). In conclusion, in the immediate postoperative period total parenteral nutrition supplemented with ornithine-α-ketoglutarate countered the decline in the muscle free glutamine. No difference in this parameter was seen between the control group and the branched chain amino acid group.*

Keywords: Postoperative, total parenteral nutrition, skeletal muscle, intracellular amino acids, branched chain amino acids, ornithine-α-ketoglutarate

Following surgical trauma protein catabolism in skeletal muscle includes alterations of the intracellular concentrations of free amino acids[1]. In man a pronounced postoperative decrease in the free glutamine concentration is accompanied by an increase in the concentrations of the free branched chain amino acids (BCAA) and of the free aromatic amino acids as well as a fall in the concentrations of the free basic amino acids[1–3].

Provision of intravenous nutritional support after elective surgery does not reverse the characteristic change in the amino acid pattern of muscle[4]. This is consistent with ribosome analyses to estimate protein synthesis in skeletal muscle, the decrease in which also remains unaffected by total parenteral nutrition (TPN)[5]. Postoperative muscle protein catabolism may be counteracted by modifications of the amino acid solution given as part of TPN. BCAA are reported to stimulate protein synthesis *in vitro*[6], but muscle protein synthesis *in vivo* in man as assessed by ribosome analysis is not preserved after operation[7]. On the other hand, ornithine-α-ketoglutarate (OAK), containing the carbon skeleton of glutamine, α-ketoglutarate, improves nitrogen balance when given along with postoperative TPN[8,9]. The decrease in muscle protein synthesis, as estimated from the concentration and size distribution of ribosomes, is also abolished[9]. Here the effects, of amino acid solutions, enriched with BCAA or supplemented with OAK and given as components of TPN after operation, upon the changes in the intracellular free amino acid concentrations of skeletal muscle following surgical trauma were evaluated.

Patients and methods

Metabolically healthy patients ($n=24$) admitted for elective cholecystectomy were studied. The characteristics of the patients and of the operative procedure are outlined in *Table 1*. Three groups of patients receiving different compositions of amino acid solutions after operation were studied (*Table 2*). The control group ($n=8$) was given a commercially available 'balanced' amino acid solution, the BCAA group ($n=8$) received a BCAA-enriched amino acid solution and the OAK group ($n=8$) was given an amino acid solution supplemented with OAK. Apart from the isonitrogenous amino acid formulae the supply of glucose, fat and electrolytes in the three groups was identical.

After an overnight fast the patients were premedicated with oxicone-scopolamine and anaesthesia was induced with thiopentone sodium, fentanyl, diazepam and pancuronium bromide. It was maintained with 70 per cent nitrous oxide in oxygen and intermittent doses of fentanyl and pancuronium bromide. All operations started before 09.00 hours. Intraoperatively, after the first muscle biopsy, the patients received 500–1000 ml of a glucose–electrolyte solution (Rehydrex®, Pharmacia Infusion, Uppsala, Sweden). As prophylaxis against thromboembolic complications, 500 ml of dextran 70, 60 g/l (Macrodex med natriumklorid®, Pharmacia Infusion) was given. Patients requiring blood transfusions or antibiotics were excluded from the study. For 3 days immediately following surgery the patients were given TPN (*Table 2*) including 135 kJ/kg body-weight/24 h of non-protein calories supplied as equal amounts of fat (Intralipid 20 per cent®, KabiVitrum, Stockholm, Sweden) and glucose (Glukos® 200 mg/ml, Pharmacia Infusion). The three groups were given equal amounts of nitrogen (0·2 g/kg body-weight/24 h). It was supplied as a commercially available amino acid solution (Vamin®, KabiVitrum), which was BCAA-enriched to 35·5 per cent of the nitrogen provided

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Table 1 *Characteristics of the patients and operative procedure*

	Control	BCAA	OAK
Sex (men/women)	3/5	5/3	2/6
Age (years)	48 (4)	60 (3)	49 (5)
Weight (kg)	72 (3)	78 (5)	69 (5)
Length (cm)	169 (2)	172 (3)	166 (2)
Operating time (min)	122 (20)	126 (20)	101 (8)
Intraoperative blood loss (ml)	330 (100)	300 (80)	240 (60)

Values are mean (s.e.m.); BCAA, branched chain amino acids; OAK, ornithine-α-ketoglutarate

Table 2 *Content in the isocaloric and isonitrogenous total parenteral nutrition given to three groups of patients after elective abdominal surgery*

	Control	BCAA	OAK
Energy	135	135	135
Total N (mg) (BCAA and OAK included)	200	200	200
Non-essential AA (mg)	830	536	711
Essential AA (mg) (BCAA included)	645	907	553
Leucine (mg)	113	334	95
Isoleucine (mg)	83	180	70
Valine (mg)	91	231	77
OAK (mg)	–	–	350

BCAA, branched chain amino acids; OAK, ornithine-α-ketoglutarate; N, nitrogen; AA, amino acids. Nutrients per kg body-weight per 24 h

(0·745 g BCAA/kg body-weight/24 h) in one group and OAK-supplemented providing 0·35 g OAK/kg body-weight/24 h (Ornicetil®, Laboratoire Jacques Logeais, Paris, France) in another group. To obtain an isonitrogenous supply the amount of commercially available amino acid solution was reduced in the BCAA and OAK groups (*Table 2*). Electrolytes, vitamins and trace elements were given as required. On the day of surgery half the amount of TPN supplied on the following days was given. No other nutrients apart from the TPN were given. The patients were allowed to drink water when the clinical condition so permitted. All nutrients of the TPN programme were supplied to the patients between 09.00 and 24.00 hours (but between 14.00 and 24.00 hours on the day of surgery). Hence, all samples were taken in the morning after an overnight fast. The nature and purpose and the risks involved in the experimental procedure were explained to the patients before obtaining their informed consent. The study protocol was approved by the Ethics Committee of the Karolinska Institute, Stockholm, Sweden.

Muscle biopsies and venous plasma samples were taken immediately after the induction of anaesthesia and on the morning of the third postoperative day. Using the percutaneous needle technique, muscle biopsy specimens were taken from the lateral portion of the quadriceps femoris muscle, approximately 15 cm above the knee[10]. The muscle tissue was dissected carefully to remove visible fat and connective tissue. The biopsy specimen with a wet weight of approximately 90 mg was divided into portions for determination of the content of free amino acids (2 × 30 mg) and of chlorides and total water (2 × 15 mg). Each piece of muscle tissue was weighed three times within 24 s on an automatic electro balance to calculate the wet weight at time zero (Cahn 29®, Cahn Instruments, Cerato, California, USA). Within 5 min after sampling, the specimens taken for amino acid analysis were frozen in liquid nitrogen and then stored at −80°C until analysed. The specimens taken for determinations of the chloride and total water content were weighed within 8 min after sampling. Thereupon they were air-dried for 6 h and then put into acid-washed quartz-glass tubes covered with parafilm until analysis. The concentrations of the free amino acids in plasma and in skeletal muscle tissue were determined by ion exchange chromatography[11] using an automated amino acid analyser (Alpha Plus®, LKB, Bromma, Sweden) and employing a DC-6® ion exchange resin (Durrum, California, USA) and lithium citrate buffers. Before analysis the muscle specimens were homogenized manually in a glass homogenizer and the proteins were precipitated in sulphosalicylic acid[12]. The intracellular free amino acid concentration of skeletal muscle was expressed in mmol per litre of intracellular water. The water distribution of the muscle tissue was estimated by the chloride method using Nernst's equation[12]. The membrane protential was approximated to be normal, −87·2 mV (Reference 13). The chloride content of the muscle specimens was determined by potentiometric titration[14].

The values are given as mean (s.e.m.). Student's *t* test for paired samples was used to compare different observations within the groups, and an unpaired *t* test to compare the differences between the groups[15].

Results

Plasma amino acids

While the BCAA increased after operation in the BCAA group, no changes were observed in the control and OAK groups. Ornithine increased significantly in the OAK group but not in the other groups (*Table 3*).

Muscle amino acids

Decreases in the free glutamine concentration ($P<0{\cdot}05$) were observed in all three groups as compared with the preoperative levels. The decline in glutamine was significantly less pronounced in the OAK group as compared with the control and BCAA groups ($P<0{\cdot}05$) (*Table 4*; *Figure 1*). The alterations in the intracellular concentrations of alanine, valine and the total sum of BCAA on the third day following surgery relative to preoperative values were significantly different in the BCAA group as compared with the control group ($P<0{\cdot}05$). The postoperative changes in the intracellular concentrations of free ornithine, arginine, the total sum of the basic amino acids (*Figure 2*) and the total sum of free amino acids were significantly different in the OAK group as compared to the control group ($P<0{\cdot}05$; *Table 4*).

Discussion

Following surgical trauma the intracellular concentrations in muscle of glutamine and of basic amino acids decrease and those of BCAA increase[1,3,4,16]. Post-traumatic protein catabolism in skeletal muscle is reflected in the characteristic change in the pattern of free amino acids. Cholecystectomy in otherwise healthy patients serves as a model for a standardized

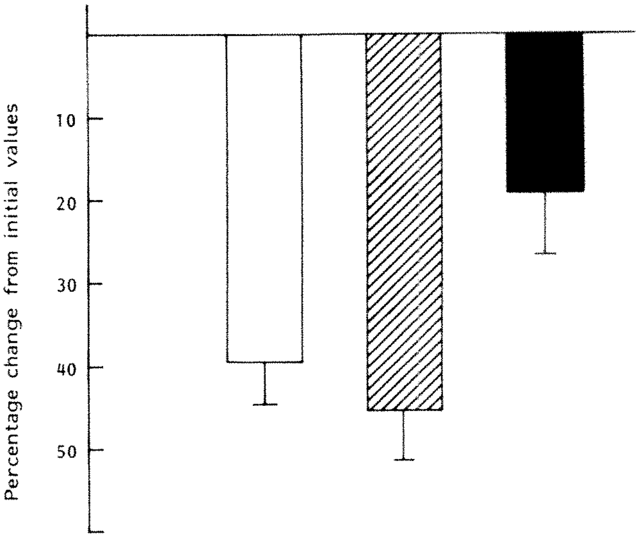

Figure 1 *The percentage decreases in the free intracellular glutamine concentration of skeletal muscle on the third day following elective abdominal surgery compared with the values before surgery. Patients received isocaloric and isonitrogenous postoperative total parenteral nutrition either containing a conventional amino acid solution* (n = 8, □), *an amino acid solution enriched with branched chain amino acids* (n = 8, ▨) *or one supplemented with OAK* (n = 8, ■). *The fall in muscle glutamine concentration was less pronounced in the OAK group than in both the control group and the branched chain amino acids group* ($P<0{\cdot}05$). *Values are given as mean(s.e.m.)*

Table 3 *Concentrations of free amino acids in plasma (μmol/l) before operation and on the third day following elective cholecystectomy*

	Control		BCAA		OAK	
	Day 0	Day 3	Day 0	Day 3	Day 0	Day 3
Taurine	85·9(10·1)	89·7(8·4)	79·8(7·3)	61·1(3·0)*	94·8(8·9)	77·2(10·9)*
Aspartic acid	6·4(0·5)	8·0(0·5)†	5·2(0·5)	4·4(0·5)§	5·6(0·2)	7·1(1·0)
Threonine	147·6(14·2)	162·9(15·2)	134·5(11·5)	139·5(9·2)	143·4(8·2)	158·4(12·3)
Serine	131·4(9·8)	137·8(7·4)	137·7(13·8)	132·6(12·9)	142·6(12·3)	152·0(10·5)
Asparagine	72·2(3·0)	70·4(7·3)	101·1(7·3)	96·9(7·0)	69·1(6·4)	58·8(3·3)
Glutamic acid	61·1(11·6)	48·3(8·3)	81·5(4·0)	44·7(5·0)‡§	73·6(13·4)	66·5(8·0)
Glutamine	659·8(21·7)	635·1(15·5)	722·6(40·3)	685·4(39·7)	612·0(47·1)	592·7(29·0)
Glycine	316·4(33·3)	283·4(26·2)	283·5(41·8)	244·2(28·9)	251·6(24·5)	226·3(26·69)
Alanine	337·6(10·6)	413·4(46·0)	348·0(31·4)	426·3(30·4)*	338·6(43·9)	427·7(43·8)†
Valine	271·8(9·5)	300·1(29·6)	276·4(20·5)	473·3(24·3)‡¶	283·1(16·6)	293·2(14·9)
Cysteine	68·4(4·4)	62·8(4·8)	83·0(4·8)	78·7(3·0)	66·5(4·3)	62·6(3·4)
Methionine	23·6(1·9)	29·8(3·4)	21·8(2·3)	37·4(3·0)‡§	28·9(2·6)	31·5(2·2)
Isoleucine	64·8(2·6)	72·6(7·9)	61·2(6·6)	99·3(6·6)†§	69·2(3·1)	72·9(6·1)
Leucine	138·6(6·4)	142·9(19·9)	130·1(12·0)	203·9(10·2)‡‖	150·2(6·8)	147·6(10·9)
Tyrosine	58·3(4·6)	71·6(9·3)	54·2(4·4)	74·0(5·9)†	59·5(3·3)	66·1(4·2)
Phenylalanine	58·3(3·5)	84·4(8·1)†	55·5(3·1)	95·4(3·0)‡	62·2(3·3)	75·9(3·9)*
Ornithine	61·8(3·2)	44·4(4·5)‡	78·6(3·4)	84·9(13·2)	53·9(4·4)	77·7(5·0)†¶
Lysine	174·5(16·2)	169·3(19·2)	210·6(13·2)	233·6(22·8)	161·9(14·6)	146·5(8·4)
Histidine	88·8(3·5)	83·3(4·9)	89·7(5·1)	90·1(5·9)	76·0(4·7)	69·3(6·7)
Tryptophan	29·3(3·0)	31·1(5·0)	41·9(5·4)	69·1(4·0)‡¶	22·2(1·8)	30·0(2·9)
Arginine	86·7(9·8)	81·3(10·2)	85·7(4·7)	94·2(11·9)	84·6(10·9)	69·7(3·4)
Essential amino acids	1006·1(46·9)	1096·4(101·4)	1027·3(70·7)	1435·2(58·6)‡‖	1024·8(47·3)	1054·7(47·2)
Total amino acids	2904·7(79·1)	2965·5(172·3)	3226·0(205·9)	3605·1(167·2)	2841·2(155·4)	2872·9(125·6)
BCAA	475·2(17·3)	515·6(55·0)	467·7(38·5)	776·6(37·4)‡¶	502·5(25·0)	513·6(31·6)

Values are mean (s.e.m.); BCAA, branched chain amino acids; OAK, ornithine-α-ketoglutarate; * *P*<0·05; † *P*<0·01; ‡ *P*<0·001 significantly different after operation as compared with the paired values obtained before surgery within the groups; § P<0·05; ‖ *P*<0·01; ¶ *P*<0·001 significantly different postoperative changes as compared with the control group

trauma with a fully developed metabolic stress response[17], which allows post-traumatic nutritional treatment to be evaluated[3,5,7,9]. Here TPN supplemented with OAK reduced the fall in the free glutamine concentration and prevented the decreases in the concentrations of the basic amino acids intracellularly in skeletal muscle as compared with conventional TPN or TPN enriched with BCAA.

The change in intracellular amino acids parallels a decrease in protein synthesis in skeletal muscle as assessed by ribosome determination[3]. Despite TPN including a commercially available amino acid solution supplying nitrogen at 0·2 g/kg body-weight per 24 h and a caloric supply of 135 kJ/kg body-weight per 24 h, the cumulative whole body nitrogen loss amounts to approximately 10 g on the third day following cholecystectomy in non-malnourished patients[3,5,7,9].

An addition of OAK to postoperative TPN maintains the protein synthesis in skeletal muscle tissue[9] and reduces the nitrogen losses[8,9] as compared with conventional TPN. An addition of glutamine to postoperative TPN also counteracts the otherwise obligatory decreases in protein synthesis and in the free glutamine concentration of skeletal muscle[3]. α-Ketoglutarate is the common determinant that may explain the effects of both glutamine and OAK on muscle free glutamine and on protein synthesis after operation. An increased need for the carbon skeleton of α-ketoglutarate after operation may be related to an altered intracellular energy metabolism in skeletal muscle during conditions of insulin resistance[18], accompanied by an enhanced need for glutamine in the small intestine[19,20]. During convalescence following trauma accompanied with sepsis the intracellular concentration of free glutamine in skeletal muscle is the last free amino acid concentration to be normalized[21].

The intracellular BCAA concentrations of skeletal muscle increase following operative trauma[1–4]. In this study the addition of OAK did not prevent the increase in BCAA reported earlier[22]. On the other hand a supply of a BCAA-enriched amino acid solution together with TPN further increased the concentration of the total sum of muscle free BCAA. Concurrently an increase in the muscle free concentration of alanine was seen, which may be due to an increased deamination of BCAA to their corresponding branched chain keto acids and production of alanine in skeletal muscle tissue[23]. The BCAA are metabolized in skeletal muscle[24] and the increased intracellular concentrations in skeletal muscle post-traumatically may be a consequence of a net degradation of muscle proteins, in which they occur in a relatively higher proportion as compared with their free intracellular concentrations[25]. The suggestion to supply them in increased amounts during conditions when their concentrations both in plasma and muscle are already elevated in order to improve muscle protein metabolism seems somewhat illogical[26]. In consequence no beneficial effect upon the muscle free amino acid concentrations was observed. Administration of postoperative TPN enriched with BCAA also fails to counteract the decrease in protein synthesis in skeletal muscle and to diminish the postoperative nitrogen losses as compared with TPN containing a conventional amino acid solution[7].

In patients operated on for colon cancer, OAK added to TPN counteracts the increase in the concentrations of BCAA and alanine and also normalizes the levels of the basic amino

Table 4 *Concentrations of free amino acids in skeletal muscle (mmol/l intracellular water) before operation and on the third day following elective cholecystectomy*

	Control		BCAA		OAK	
	Day 0	Day 3	Day 0	Day 3	Day 0	Day 3
Taurine	26·18(2·14)	25·86(1·93)	20·18(2·48)	23·92(2·57)§	20·42(2·25)	21·34(2·79)
Aspartic acid	1·98(0·18)	1·82(0·20)	2·04(0·11)	1·78(0·16)	2·10(0·18)	1·89(0·34)
Threonine	1·15(0·11)	1·42(0·17)*	1·17(0·06)	1·84(0·24)*	1·12(0·11)	1·12(0·11)
Serine	1·30(0·23)	1·39(0·10)	1·28(0·19)	1·90(0·29)	1·11(0·07)	1·60(0·16)*
Asparagine	0·51(0·07)	0·48(0·09)	0·66(0·09)	0·84(0·10)	0·65(0·08)	0·63(0·08)
Glutamic acid	4·83(0·55)	4·11(0·63)	4·70(0·43)	3·91(0·51)	4·49(0·14)	4·52(0·47)
Glutamine	26·85(1·07)	16·28(1·01)‡	24·09(1·66)	13·18(1·16)‡	23·65(1·58)	19·19(1·81)*§
Glycine	2·56(0·17)	2·61(0·23)	2·60(0·20)	3·56(0·60)	2·21(0·21)	2·23(0·16)
Alanine	5·45(0·28)	5·50(0·45)	4·53(0·27)	6·80(0·86)†§	3·71(0·24)	4·67(0·48)
Valine	0·34(0·02)	0·48(0·05)*	0·32(0·02)	0·82(0·11)†‖	0·33(0·05)	0·52(0·10)*
Isoleucine	0·05(0·01)	0·08(0·02)	0·07(0·02)	0·09(0·02)	0·06(0·01)	0·14(0·02)†
Leucine	0·32(0·02)	0·46(0·06)*	0·30(0·04)	0·61(0·06)†	0·21(0·02)	0·38(0·05)*
Tyrosine	0·15(0·02)	0·27(0·06)*	0·14(0·04)	0·25(0·06)	0·10(0·02)	0·18(0·04)†
Phenylalanine	0·12(0·02)	0·22(0·02)‡	0·12(0·02)	0·25(0·04)†	0·13(0·02)	0·18(0·02)
Ornithine	0·33(0·04)	0·24(0·04)†	0·35(0·09)	0·27(0·05)	0·34(0·05)	0·91(0·13)†§
Lysine	1·18(0·13)	1·00(0·13)	1·33(0·18)	0·80(0·10)*	1·23(0·18)	1·45(0·12)
Histidine	0·39(0·02)	0·28(0·02)‡	0·51(0·06)	0·44(0·07)	0·45(0·01)	0·48(0·05)
Tryptophan	7·56(0·78)	6·39(0·60)*	7·59(0·53)	8·03(1·07)	6·61(0·83)	6·72(0·79)
Arginine	0·70(0·09)	0·45(0·09)‡	0·65(0·13)	0·42(0·07)	0·66(0·07)	0·82(0·13)§
Essential amino acids	3·17(0·21)	3·52(0·33)	3·24(0·27)	4·50(0·52)*	3·08(0·33)	3·79(0·35)
Total amino acids	48·21(1·38)	37·05(2·09)‡	44·86(2·09)	37·76(3·68)*	42·55(1·99)	40·91(3·34)§
BCAA	0·71(0·04)	1·02(0·11)*	0·69(0·06)	1·52(0·17)†§	0·60(0·08)	1·02(0·15)*
Basic amino acids	2·20(0·20)	1·72(0·17)*	2·49(0·25)	1·66(0·25)*	2·33(0·24)	2·71(0·18)§

Values are mean (s.e.m.); BCAA, branched chain amino acids; OAK, ornithine-α-ketoglutarate; * $P<0·05$; † $P<0·01$; ‡ $P<0·001$ significantly different after operation as compared with the paired values obtained before surgery within the groups; § $P<0·05$; ‖ $P<0·01$; ¶ $P<0·001$ significantly different postoperative changes as compared with the control group

acids as compared with a control group[22]. On the other hand, the cited study reveals no statistically significant effect upon the postoperative depletion of muscle free glutamine in the patients receiving OAK as compared with a control group. The differences in the results regarding the postoperative effects upon BCAA and glutamine levels between these two studies may be due to different amounts of nitrogen supplied (0·15 g/kg per 24 h *versus* 0·20 g/kg per 24 h, the difference in the amount of OAK (25 g per 24 h *versus* 0·35 g/kg per 24 h), the different statistical methods used, and to the different categories of patients included. The nutritional status of the patients with colon cancer is not defined[8,22] whereas the patients here with gallstone disease were non-malnourished.

OAK exerts a stimulating effect upon insulin release[27] and reduces the negative arterio-venous differences in glycine, lysine and alanine across the leg in burn patients[28]. The two compounds of OAK, ornithine and α-ketoglutarate have important functions in amino acid and urea metabolism. In the urea cycle ornithine is produced after the hydrolysation of arginine to ornithine and urea by the action of arginase. Excess amounts of ornithine inhibit the action of arginase and lead to a lower production of urea and, concurrently, an enhanced production of proline via increased action of ornithine aminotransferase[29]. Thus an addition of ornithine in the form of OAK has been suggested to have a nitrogen-sparing effect[22].

The present study concentrates on skeletal muscle, which constitutes the largest pool of intracellular free amino acids in human subjects. In a normal man with a body-weight of 70 kg the total free amino acid content is estimated to be between 80

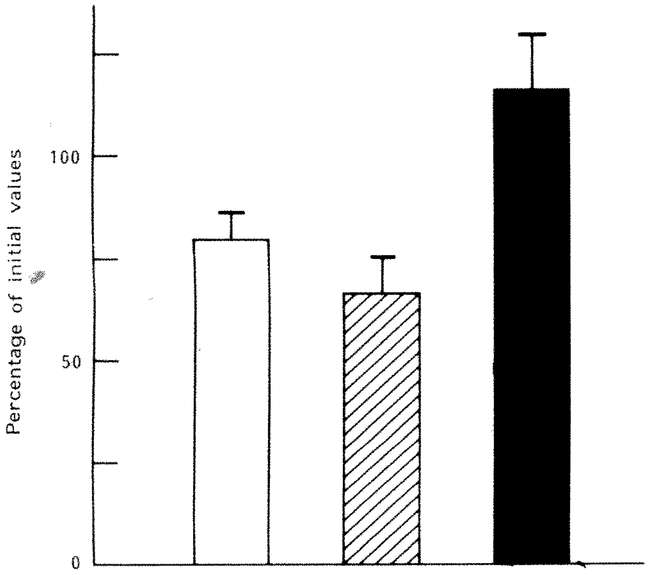

Figure 2 *The sum of the intracellular concentrations of the free basic amino acids (lysine, histidine and arginine) in skeletal muscle on the third postoperative day as a percentage of the preoperative values. The concentration of the free basic amino acids in muscle decreased after operation in the control group* (n = 8, ☐) *and in the branched chain amino acids group* (n = 8, ▨), *but not in the OAK group* (n = 8, ■), *in which the level was preserved. Values are given as mean(s.e.m.)*

and 90 g[12]. Most amino acids occur in much higher concentrations intracellularly than in plasma with the exception of the BCAA, phenylalanine and tyrosine, which have an intra-extracellular gradient of less than two. The intracellular amino acid pattern does not fluctuate as rapidly as that of the plasma free amino acids. The intracellular amino acid concentrations are influenced by a combined effect of the affinity to the transport systems, the net protein turnover, plasma concentrations of amino acids and the leakage across the cell membrane[30]. The steady state of the intracellular amino acid pattern mirrors both physiological and pathophysiological changes in muscle protein metabolism with characteristic changes for growth, ageing, trauma, sepsis, starvation, uraemia and diabetes[30].

An increase in the concentration of free phenylalanine in plasma was seen in all three groups which is a constant finding following trauma[31]. The concentrations of BCAA increased in the BCAA group and that of ornithine increased in the OAK group. However the plasma amino acid determination only gives a momentary value of a rapidly changing process. The importance of plasma amino acid alterations after operation should therefore not be overemphasized[1].

It is essential to limit the decrease in the intracellular glutamine concentration of skeletal muscle after surgical trauma. A large decrease accompanies severe muscle protein catabolism and constitutes an alarming prognostic sign in septic surgical patients[32,33]. In conclusion, a postoperative supply of TPN enriched with OAK reduced the loss of free glutamine in skeletal muscle. This effect was not seen when giving TPN enriched with BCAA after operation. Muscle protein catabolism may be counteracted by supplying α-ketoglutarate in the form of OAK given as a component of TPN after operation.

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Self protection in surgery: the use of double gloves

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This study assesses the perforation rate of single and double gloves and thus the extent to which double gloving protects the surgeon from diseases transmissible from the patient. We have also investigated whether double gloving offers the patient extra protection by reducing wound sepsis. Two hundred adult hernia repairs were performed, the first 100 single gloved and the second 100 double gloved. Glove perforation rates were not significantly different between single gloves and the outer of the double gloves. Although 46 of 400 outer gloves were perforated there were only 15 inner glove perforations and only eight of these matched the outer perforations. The percentage of operations in which the latex protective barrier was breached was reduced from 31 per cent when the surgeon wore single gloves to 8 per cent with double gloves. Wound sepsis was not increased by glove perforation nor reduced by double gloving. While careful technique remains mandatory we conclude that double gloving offers increased protection to the surgeon operating on high risk infectious cases.

Keywords: Glove perforation

The practice of operative surgery is for the health of the patient, but the emergence of transmissible viruses such as hepatitis B and human immunodeficiency virus has led surgeons to consider their own safety. Barrier techniques have been recommended when handling potentially infected tissues or fluids[1] and for this reason surgical teams have taken to wearing two gloves on each hand when operating on high risk patients.

Perforation of surgical gloves by sharp instruments is a common event[2]. The most common cause of perforation is a needle prick. A sharp needle may perforate two layers of latex gloves as easily as one and it is uncertain whether double gloving effectively protects against such injury. It has been argued that the decreased sensitivity and dexterity caused by wearing double gloves actually increases the likelihood of injury[3]. We have compared glove perforation rates during hernia repair when surgeons wore single gloves to those when double gloved. The purpose of this investigation was to ascertain whether double gloving offered extra protection to the surgeon from the patient and extra protection to the patient by reducing wound infection.

Patients and methods

This study was undertaken on 200 adult patients having hernia repair. The first 100 consecutive hernia repairs were performed with surgeons and assistants wearing single gloves in the usual way. A further 100 hernia operations were done with surgeon and assistants double gloved. Only Biogel® gloves (Regent Dispo, LRC Products Ltd., London, UK) were used. Following operation all gloves were tested for perforations by filling them with water under pressure and observing for leaks. This method has proved effective in detecting perforations[4]. The surgeons were asked before testing if they thought that perforation had occurred. The wounds were inspected for signs of infection at 7–10 days. No antibiotic prophylaxis was used.

Results

Incidence of glove perforation

Glove perforation among the 400 gloves used in the 100 single gloved hernia repairs occurred in 51, an overall incidence of 12·8 per cent (surgeons 15 per cent, assistants 10 per cent). In the double gloved series, the number of perforations in the 400 outer gloves was 46 or 11·5 per cent (surgeons 16 per cent, assistants 7 per cent; *Table 1*). Perforations occurred in 15 of the 400 inner gloves (3·8 per cent). In seven cases the inner glove was perforated despite an intact outer glove. In the other eight cases the inner glove perforations matched outer glove perforations. Operators were unaware of these perforations in 50 per cent of cases when single gloved and in 42 per cent when double gloved. Perforations occurred in the glove on the non-dominant hand of the surgeon in 80 per cent of the cases whether single or double gloved. A glove perforation occurred in 31 per cent of single gloved operations and 39 per cent of double gloved operations, but in only 8 per cent of double gloved operations was the latex barrier breached by matched inner and outer punctures.

Effect of glove perforation on wound sepsis

The effects of glove perforation and double gloving on wound sepsis are summarized in *Tables 2* and *3*. Wound sepsis rates were similar whether surgeons wore single gloves (10 per cent) or double gloves (8 per cent). Perforation of gloves, whether single or double, did not influence wound sepsis.

Table 1 *Percentage of perforations in 400 outer and 400 inner gloves worn during 100 hernia repairs*

	Outer perforation (%)	Matched outer and inner perforations (%)	Inner alone (%)
Surgeon	16	2·5	2
Assistant	7	1·5	1·5
Overall	11·5	2·0	1·8
Operations	39	8	0

Table 2 *Relation between glove perforations in 100 single gloved hernia repairs and wound sepsis*

	Single glove perforation	
	Present	Absent
Wound sepsis		
Present	4	6
Absent	27	63

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Table 3 *Relation between matched glove perforations in 100 double gloved hernia repairs and wound sepsis*

	Matched glove perforations	
	Present	Absent
Wound sepsis		
Present	1	7
Absent	7	85

Discussion

The practice of double gloving decreases tactile sensation and manual dexterity. It may also be uncomfortable for the surgeon, especially if the gloves are pulled tightly over the finger tips. For these reasons the surgeon removed the outer glove during 26 per cent of operations in one study[5]. It has been suggested that the decrease in dexterity may actually increase the likelihood of self injury with a sharp instrument or needle[3]. Previous studies of glove perforation have included a range of operations carrying different risks of glove perforation and cannot, therefore, be directly compared. In this report we studied hernia repair only, so that differences between single and double gloving would be more easily assessed. The outer glove perforation rate of 11·5 per cent in this study is not statistically significantly different from the 12·8 per cent rate for single gloves or from the 11 per cent rate found in a recent report[5], particularly as the operations were not exactly comparable. Thus there is little evidence that glove perforation is more likely to occur when wearing two pairs of gloves.

In the majority of cases in which outer glove perforation occurred, the inner glove remained intact, maintaining the barrier between surgeon and patient. This barrier was breached in 31 per cent of single gloved operations, but with double gloves this was reduced to 8 per cent. The rate of perforation of the inner glove alone was 1·8 per cent. These gloves may have been perforated before use and this figure correlates with previous experience[4]. Double gloving significantly minimizes the risks of a breach of the latex barrier being present before use.

It has been shown that breach of the barrier between the surgeon's prepared hands and the patient does not increase the rate of wound sepsis[4] and this was confirmed by the present study. Such a breach does, however, expose the surgeon or assistant to the patient's tissue and body fluids and thus to potential pathogens. Peroperative changing of damaged gloves can reduce this exposure but in half the cases the operator is unaware of glove damage. Electronic devices that can detect glove damage are being evaluated[6].

Double gloving reduces the incidence of accidental exposure at the expense of dexterity and comfort. A high incidence of perforation occurring in the surgeon's non-dominant hand suggests that wearing two pairs of gloves on that hand alone would offer increased protection to those concerned about loss of dexterity. No barrier method offers complete protection for surgeons using sharp instruments and the greatest attention must still be paid to careful operative technique. Nevertheless, we have demonstrated that, while wearing double gloves offers no extra protection to the patient, it significantly reduces the risk to the surgeon.

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Efficacy of continuous extrapleural intercostal nerve block on post-thoracotomy pain and pulmonary mechanics

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To assess the efficacy of continuous extrapleural intercostal nerve block on postoperative pain and pulmonary function, a prospective, randomized, double-blind, placebo-controlled trial was conducted on 56 patients undergoing elective thoracotomy. Infusion was started before closing the chest and was continued for 5 days. Subjective pain relief was assessed on a linear visual analogue scale. Pulmonary function was measured on the day before operation and daily for 5 days. There were 29 patients in a group which received bupivacaine and 27 in a control group which received saline. The bupivacaine group had lower pain scores ($P<0\cdot01$) *and required less papaveretum* ($P<0\cdot01$) *than the control group. Forced vital capacity, forced expiratory volume in 1 s and peak expiratory flow rate were maximally reduced at 24 h to median values of 56, 60 and 57 per cent, respectively, of preoperative control values in the bupivacaine group, and to 25, 30 and 32 per cent in the control group. These differences are highly significant* ($P<0\cdot01$). *Restoration of pulmonary function was superior in the bupivacaine group* ($P<0\cdot01$). *There were no infusion-related complications. After thoracotomy, continuous intercostal blockade with bupivacaine is a safe and effective method of pain relief which reduces the early loss of postoperative pulmonary function significantly and more rapidly restores respiratory mechanics.*

Keywords: Continuous intercostal nerve block, thoracotomy, analgesia, postoperative pulmonary mechanics

Thoracotomy causes severe postoperative pain and marked impairment of pulmonary function[1]. These changes are most exaggerated in the elderly, the obese, in smokers and in those with pre-existing cardiopulmonary disease[2]. Pain in the early post-thoracotomy period is the most important factor responsible for ineffective ventilation, ineffectual cough and impaired ability to breath deeply and sigh, leading to atelectasis, hypoxaemia, infection and respiratory distress[3,4]. Inadequate analgesia results in needless suffering and may prevent early ambulation and deep breathing. Effective analgesia minimizes impairment of pulmonary function, aids in its recovery, and may prevent some postoperative pulmonary complications[5,6].

The unilateral nature of most thoracic surgical procedures makes pain control by intercostal nerve block feasible. Several prospective randomized studies have shown that intraoperative and percutaneous intercostal nerve blocks with bupivacaine aid recovery of ventilatory function after thoracotomy[6–11]. Continuous infusion of bupivacaine through an indwelling epidural catheter placed extrapleurally at thoracotomy overcomes the need for repeated intercostal blocks[12]. The present study is a randomized, controlled, trial designed to assess the effects of continuous intercostal nerve block on postoperative pain and pulmonary function in patients undergoing elective thoracotomy.

Patients and methods

Study design and surgical technique

All patients undergoing elective thoracotomy gave informed consent and were admitted to the trial. Before operation, patients were instructed in the use of the Respirodyne® (Chesebrough-Pond's Ltd, London, UK)[13] and the linear visual analogue scale for pain assessment. Those who were treated with non-steroidal anti-inflammatory drugs and opiates before operation, and those who had an additional incision or procedure (e.g. Ivor–Lewis, double thoracotomy), were excluded. All patients had a standard anaesthetic using a double lumen endobronchial tube and one-lung ventilation.

Towards the end of the operation, before the closure of the thorax, the parietal pleura was peeled medially starting at the thoracotomy space. The resulting pocket between the posterolateral pleura and the chest wall was extended from the posterior wound margin on to the vertebral bodies and for two intercostal spaces above and two below. A percutaneous paravertebral epidural cannula was inserted, via a 16-gauge disposable Tuohy® (Portex Ltd., Hythe, UK) needle, 5 cm below the wound edge and lateral to the border of erector spinae. The cannula was positioned such that it lay against the costovertebral joint within this pocket (*Figures 1* and *2*). The parietal pleura was then simply reattached to the posterior edge of the wound and the catheter was secured. All epidural catheters had a bacterial filter in line[12].

Each patient was randomized, by drawing a card in theatre, to receive either saline or bupivacaine. The patient then received 20 ml of the appropriate infusate via the cannula. On returning to the ward, those in the bupivacaine group received an infusion of 5–10 ml/h 0·5 per cent plain bupivacaine (5 mg/ml) according to weight (5 ml/h for 50–59 kg, 6 ml/h for 60–69 kg, 7 ml/h for 70–79 kg, 8 ml/h for 80–89 kg, 9 ml/h for 90–99 kg and 10 ml/h for those over 100 kg. Those in the saline group received similar volumes of normal saline according to weight. The infusions were continued until the morning of the sixth postoperative day. All patients had access, on request, to intramuscular papaveretum (10–15 mg according to weight) and/or rectal diclofenac sodium during the first 48 h, and thereafter to oral Co-Codamol® (Sterwin Medicine, Guildford, UK) and/or rectal diclofenac sodium. No attempt was made to withhold requested analgesic. The randomization code was available to the investigators at all times in case of emergency, but personnel taking measurements and setting up the infusion were kept 'blind'.

Postoperative assessment

Subjective pain relief. Postoperative pain was assessed by patients themselves on a linear visual analogue scale (a 10-cm ungraduated

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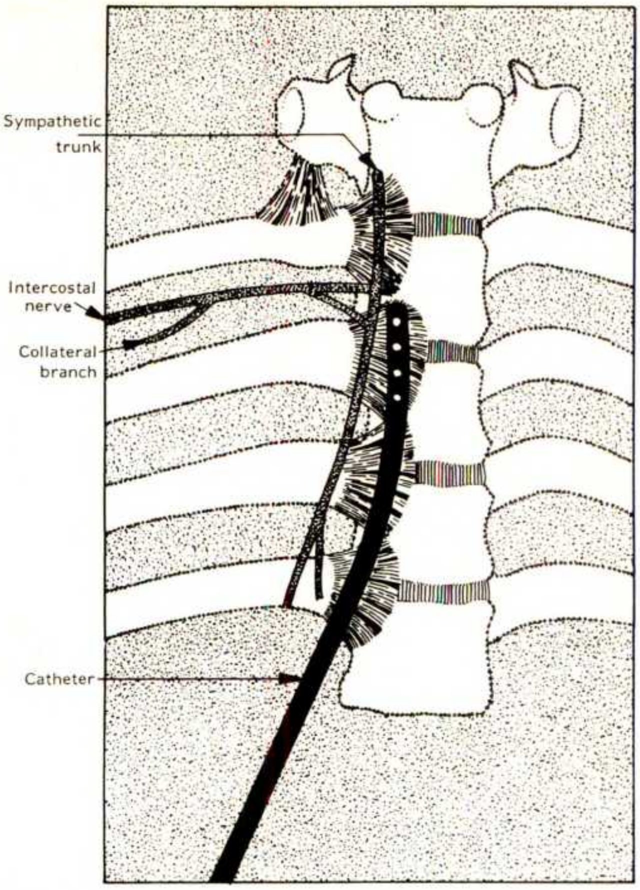

Figure 1 *Schematic diagram showing longitudinal lie of the catheter*

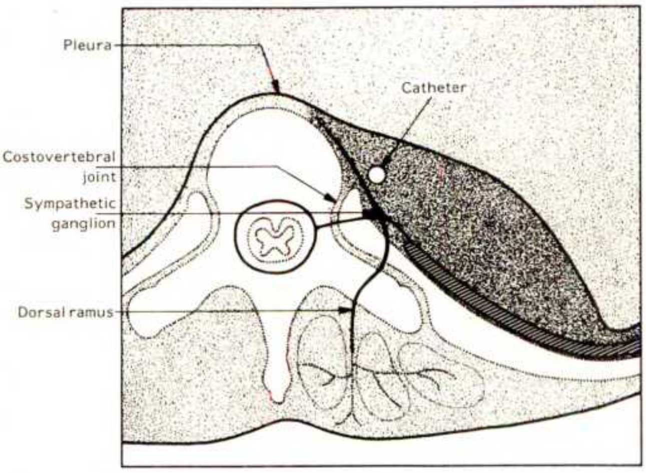

Figure 2 *Diagram showing the lie of the extrapleurally placed epidural catheter in relationship to the ribs, pleura and vertebrae in sagittal plane. The darkly stippled area represents the accumulation of local anaesthetic solution in the paravertebral space*

line). The left-hand margin, corresponding to a score of zero, represented no pain, while the right-hand margin, corresponding to a score of ten, represented the worst pain imaginable. Each patient's pain score was recorded at recovery from anaesthetic, and at 1, 4, 8, 16, 24, 32, 48, 72 and 120 h after surgery. In addition, the number of administered doses and the total amounts of papaveretum, rectal diclofenac sodium and Co-Codamol were recorded for each patient.

Objective respiratory function. Before surgery and on each morning of the first 5 days after surgery, forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and peak expiratory flow rate (PEFR) were measured in the sitting position using the Respirodyne. Results were expressed as a percentage of the preoperative values. As in previous studies of post-thoracotomy pulmonary function[5,8,9], preoperative function was used as a baseline even in those patients who had lung resections.

Statistics

Results were analysed using the Kruskal–Wallis one-way analysis of variance by ranks and the Mann–Whitney *U* test to determine statistical significance.

Results

The groups were comparable in age, sex ratio, smoking habits, body-weight, height, site and type of operation. Patient characteristics and surgical procedures are summarized in *Table 1*. There were no infusion-related complications.

Pain relief

The bupivacaine group had significantly better ($P<0{\cdot}01$) pain relief throughout the study period, as determined by linear analogue pain score (*Figure 3*). In addition, the postoperative papaveretum requirement was significantly decreased ($P<0{\cdot}01$) in the bupivacaine group. None of the patients in this group needed rectal diclofenac sodium. *Table 2* summarizes the postoperative analgesic requirement in the first 48 h.

Postoperative pulmonary function

In the bupivacaine group the median values (interquartile range) of FVC, FEV_1 and PEFR were reduced at 24 h to 56 per cent (range 52–68 per cent) (*Figure 4*), 60 per cent (range 54–68 per cent) (*Figure 5*) and 57 per cent (range 49–67 per cent) (*Figure 6*), respectively, of preoperative control values. The equivalent values in the control group were 25 per cent (range 17–33 per cent) (*Figure 4*), 30 per cent (range 20–38 per cent) (*Figure 5*) and 32 per cent (range 24–35 per cent) (*Figure 6*). The differences between groups were highly significant ($P<0{\cdot}01$). These values, although improving, did not return to preoperative levels by the fifth day after surgery in either group (*Table 3*). The recovery rate appeared to be similar but the levels of FVC, FEV_1 and PEFR remained significantly poorer in the saline group ($P<0{\cdot}01$) throughout the time period studied. Clinically and radiologically detected pulmonary complications occurred in 11 of the 56 patients. Nine were in the control group and two were in the bupivacaine group. All patients showed a maximum loss of lung function at 24 h (*Table 3*). However, those with pulmonary complications showed a further significant fall (greater than 20 per cent) in FVC, FEV_1 and PEFR on a subsequent day when reviewed retrospectively.

Table 1 *Characteristics of patients and surgical procedures*

	Bupivacaine group ($n=29$)	Control (saline) group ($n=27$)
Age (years)*	58 (21–69)	54 (21–68)
Sex (m:f)	26:3	20:7
Side		
Left thoracotomy	18	17
Right thoracotomy	11	10
Procedure		
Lung resection		
Lobectomy	11	8
Pneumonectomy	4	6
Lung biopsy	2	1
Oesophageal surgery		
Antireflux procedure	7	8
Oesophagectomy	4	3
Heller myotomy	0	1
Excision of leiomyoma	1	0

* Mean (range in parentheses)

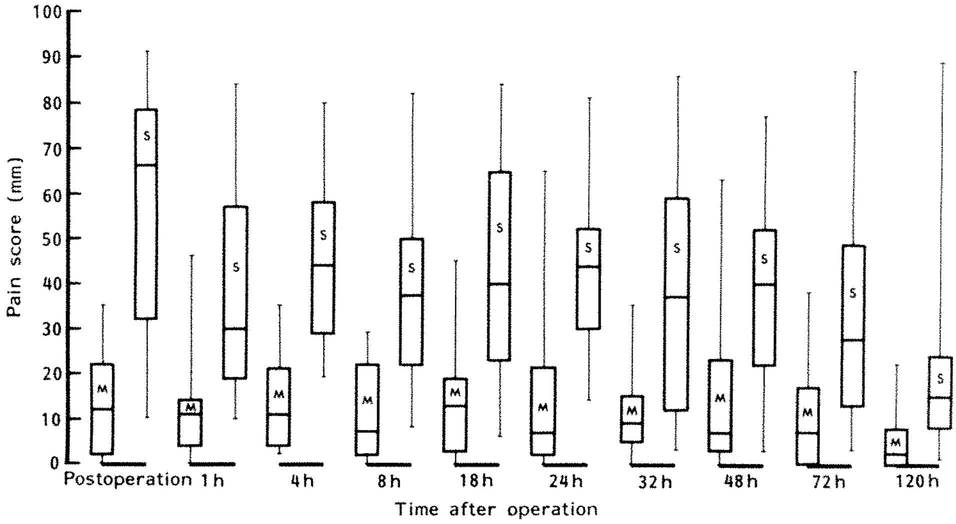

Figure 3 *'Box and whisker' plot of pain scores during the first 5 days after operation. The accumulated pain scores were significantly lower* ($P<0\cdot01$) *in the bupivacaine (M) group throughout the study period than in the saline control (S) group*

Table 2 *Postoperative analgesic requirements in the first 48 h*

	Bupivacaine group (*n*=29)	Control (saline) group (n=27)	*P*
No. of patients requiring no opiate supplementation*	17 (59)	0	<0·01 (binomial)
Opiate requirement (mg)†	14 (0–126)	136 (70–200)	<0·01 (Kruskal–Wallis)
No. of patients requiring no rectal diclofenac*	29 (100)	11 (41)	<0·01 (binomial)

* Percentages are given in parentheses; † mean (range in parentheses)

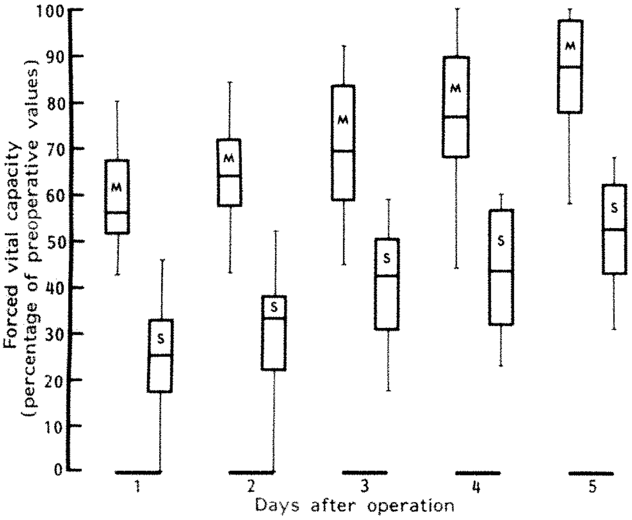

Figure 4 *'Box and whisker' plot of the percentage reduction in forced vital capacity (FVC) values in the first 5 days after thoracotomy. There was a significant difference* ($P<0\cdot01$) *between the saline control (S) and bupivacaine (M) groups at each measurement time*

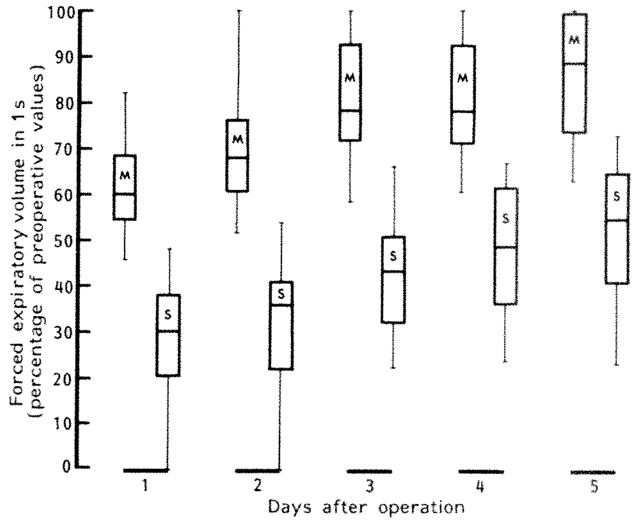

Figure 5 *'Box and whisker' plot of forced expiratory volume in 1 s* (FEV_1) *values as percentages of preoperative values. There was a significant difference in the rate of recovery* ($P<0\cdot01$) *between the bupivacaine (M) and the saline control (S) groups*

Discussion

This study confirms the findings of other investigators that there are marked alterations in pulmonary function following thoracotomy[14,15]. One of the earliest changes in postoperative ventilatory mechanics is the marked reduction in effort-dependent lung volumes. This occurs before changes in the functional residual capacity (FRC) can be measured and is an important factor in the development of pulmonary dysfunction[15]. More importantly, the reduction in FRC is not accompanied by any significant alteration in the closing volume, resulting in airway closure during tidal breathing[16]. This leads to hypoxaemia due to increased venous admixture from regional ventilation perfusion inequality and shunting of pulmonary capillary blood through closed alveoli. After thoracotomy, patients are unable or unwilling to inspire deeply. The reduced inspiratory capacity limits the ability to cough effectively. Impaired lung volumes, particulary FRC, ventilatory mechanics and oxygenation are the consequences of this shallow monotonous breathing without periodic maximal inflation[4,14,15]. Sighing reverses these changes[14,17].

Once a segment has developed airway closure and atelectasis, air movement in the bronchus to that segment and secretions tend to pool there and become a focus for infection. Postoperative pulmonary complications correlate positively with the decrease in ventilatory efficiency[14,15,18]. These changes may be modified but not prevented[1,2]. The greater the decrease in FRC, FVC, FEV_1 and PEFR, the more likely it is that a major pulmonary complication will occur[14,15,18]. our finding that the deterioration of effort-dependent lung volumes is associated with pulmonary complications confirms those observations. Pain is the most important factor responsible for the decrease in respiratory reserve after operation and effective postoperative analgesia improves respiratory mechanics[5,6,8].

Narcotic drugs given either by the conventional intramuscular route or by continuous, patient-controlled infusion are used widely and have the well known disadvantages of causing drowsiness, nausea, vomiting, hypotension and respiratory depression[19,20]. Paradoxical breathing and obstructive apnoea are the predominant ventilatory disturbances associated with narcotics, and they are associated with reduction of lung volume and arterial hypoxaemia[19]. These changes are exaggerated in patients with chronic obstructive airway disease[21] or gross obesity and in patients recovering from thoracotomy[22].

Regional anaesthesia, which includes epidural anaesthesia, cryoanalgesia[23], intercostal nerve block[7] and paravertebral block[24], has the advantage of providing analgesia without central respiratory depression. Thoracic epidural analgesia using either narcotic or local anaesthetic agents has already been shown to provide effective postoperative analgesia and to improve respiratory mechanics[5] but, because of the difficulties in providing adequate staffing for the necessary frequent observation, epidural analgesia is difficult to apply to large numbers of surgical patients.

Much of the pain after thoracotomy is due to straining from rib retraction of the ligaments of the costovertebral and costotransverse joints and the posterior spinal muscles[24]. Such pain is mediated by posterior primary rami[24]. Thoracotomy pain may also arise from the visceral pleura and organs and be conducted via afferent fibres in sympathetic nerves[25,26]. Cryoprobe neurolysis of intercostal nerves does not include posterior primary rami and sympathetic fibres and so does not provide complete postoperative pain relief[26,27]. Effort-dependent lung volumes following thoracotomy were found to be similar at 24 h in patients receiving cryoanalgesia and in controls[28]. Paravertebral blockade using local anaesthesia is more effective than pure intercostal block, since the former also blocks the posterior primary rami and sympathetic fibres[24], and unilateral blockade of the sympathetic chain in the paravertebral space may also reduce the hormonal and neural metabolic response to surgery[30]. The segmentation of intercostal nerves into small bundles lying freely in the paravertebral space, without any enclosing fascial sheath, exposes the nerves favourably for blockade[31]. While many authors have demonstrated the safety of the percutaneous approach to the paravertebral space[31–34], placing the catheters under direct vision at thoracotomy is easier and more accurate. The use of methylene blue peroperatively and radiological contrast on the fifth day of the infusion has demonstrated that the mechanism of action is via the paravertebral spread of anaesthetic[29].

Although spread to the extradural space has also been demonstrated with paravertebral block[35], making extradural blockade and hypotension a possible complication[32], such problems have rarely been reported. We have not encountered such a complication in over 300 patients. A bupivacaine dose of 2 mg/kg should not be exceeded in any 4-h period, by extrapolation from animal experiments[36]. However, as bupivacaine is more than 90 per cent bound to plasma proteins at concentrations of 1 μg/ml, the systemic toxicity is lower in humans than might be predicted from acute toxicity studies in animals[37], and the results of many studies indicate that a dose of 3 mg/kg can be used in children and adults without demonstrable side-effects[38,39]. Systemic toxicity following the injection of local anaesthetic occurs infrequently[40]. In the

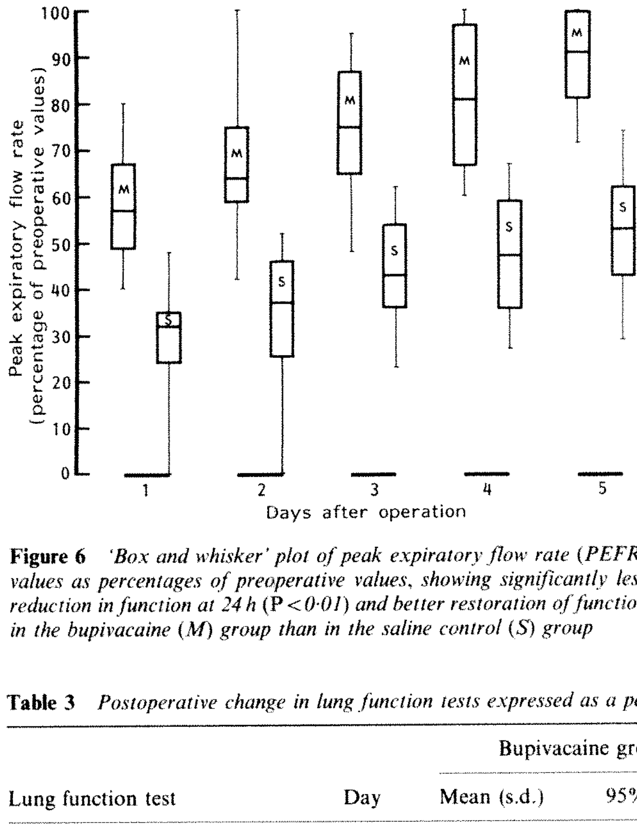

Figure 6 *'Box and whisker' plot of peak expiratory flow rate (PEFR) values as percentages of preoperative values, showing significantly less reduction in function at 24 h* ($P < 0.01$) *and better restoration of function in the bupivacaine (M) group than in the saline control (S) group*

Table 3 *Postoperative change in lung function tests expressed as a percentage of preoperative values*

		Bupivacaine group ($n = 29$)		Control (saline) group ($n = 27$)		
Lung function test	Day	Mean (s.d.)	95% confidence limit	Mean (s.d.)	95% confidence limit	P
Forced vital capacity	1	58 (9)	3·3	25 (12)	4·7	<0·01
	2	65 (10)	4·0	31 (12)	4·9	<0·01
	3	70 (13)	5·1	41 (11)	4·5	<0·01
	4	79 (17)	6·3	45 (12)	5·1	<0·01
	5	89 (18)	6·7	52 (11)	4·6	<0·01
Forced expiratory volume in 1 s	1	61 (9)	3·4	28 (14)	5·4	<0·01
	2	70 (12)	4·8	33 (13)	5·0	<0·01
	3	76 (12)	4·8	44 (13)	5·2	<0·01
	4	83 (13)	5·1	48 (13)	5·2	<0·01
	5	90 (14)	5·6	52 (13)	5·7	<0·01
Peak expiratory flow rate	1	59 (11)	4·1	30 (10)	3·9	<0·01
	2	69 (15)	6·0	35 (13)	5·2	<0·01
	3	76 (14)	5·5	45 (11)	4·4	<0·01
	4	88 (26)	9·9	48 (13)	5·3	<0·01
	5	92 (12)	4·4	52 (13)	5·3	<0·01

present study the rate of infusion was in the recommended range of 2 mg/kg over 4 h, but continuously for 5 days. At this dosage we have observed no toxic reaction.

This study has demonstrated that pulmonary function was significantly better in patients receiving continuous intercostal nerve block with bupivacaine via an extrapleural catheter inserted at thoracotomy than in patients receiving conventional analgesia and mock nerve block. The incidence of postoperative pulmonary complications was reduced in the former patients. The technique is a safe and reliable method of providing analgesia after thoracotomy without any significant side-effects.

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Short note

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Paget's disease without a palpable mass in the breast

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The infiltration of breast carcinoma cells into the epidermis of the nipple along mammary ducts without any direct invasion is called Paget's disease of the breast. Paget's disease was first described by Sir William Paget in 1874[1]. The infiltration can either be microscopic or gross in the form of scaling, erythema, erosion or ulceration. In advanced cases ulceration may extend to the skin of the areola. When the primary tumour is palpable it is quite easy to identify the nipple lesion as Paget's disease, but if there is a nipple lesion without a palpable mass in the breast the lesion is often diagnosed as dermatitis which causes delay in diagnosis and treatment.

Over a 28-year period, among 937 patients with breast carcinoma, ten patients with Paget's disease of the breast without a palpable mass in the breast were found and studied retrospectively.

Patients and methods

Between December 1959 and December 1987, among 937 patients with breast carcinoma, 23 were found to have Paget's invasion of the nipple. Three of these patients were not operated upon due to the advanced stage of the breast carcinoma and one patient refused the operation. A Halsted type radical mastectomy was performed for the remaining 19 patients. In ten patients the nipple lesion was the only sign without a palpable mass in the breast. The remaining 13 patients had a palpable mass in the breast besides the nipple lesion.

Results

The patients without a palpable mass in the breast were all females ranging in age from 42 to 62 years (mean 51 years). The delay in presentation ranged from 1 week to 3·5 years with a mean of 11·1 months (*Table 1*). The time from onset of the symptoms to diagnosis was 1·5 months to 6 years (mean 25·1 months).

In all patients the diagnosis of Paget's invasion was made by nipple biopsy. The lesion was in the left breast in seven and in the right breast in three patients.

When radical mastectomy specimens were inspected, macroscopic tumour ranging in diameter from 0·3 to 1·2 cm was found in five. In the remaining five the tumour was only identifiable microscopically. In two patients the tumour was multicentric. The carcinoma was located in the upper outer quadrant in three, lower outer quadrant in two, lower inner quadrant in four and upper inner quadrant in one patient.

All ten patients on clinical examination were apparently free from nodal involvement, but microscopic examination revealed metastasis to the axillary lymph nodes in two patients. Postoperative radiotherapy was given to one patient who had seven metastatic lymph nodes in the axilla. The remaining nine patients did not receive any adjuvant therapy following radical mastectomy.

One of the patients died of disseminated disease in the fourth year after operation. No evidence of local recurrence or distant metastasis is detected in the remaining patients who have been followed up for 1–19 years (*Table 1*).

Six patients with no palpable mass in the breast were initially diagnosed and treated as having dermatitis of the nipple, one of whom showed complete healing of the nipple lesion after 1 month. Recurrence of the nipple lesion after 2 months led us to biopsy the nipple and Paget's invasion was then found.

Table 1 *Patients with Paget's disease without a palpable mass in breast*

Patient no.	Age (years)	Time from first symptom to presentation	Time from first symptom to diagnosis	Treatment	Axillary lymph node metastasis	Postoperative follow-up
1	42	1 week	6 months	Right RM	(−) 0/14	No recurrence in 19th year
2	45	3 years	3 years	Right RM	(+) 1/25	No recurrence in 16th year
3	52	3 months	7 months	Left RM + RT	(+) 7/26	No recurrence in tenth year
4	48	1 month	2·5 years	Left RM	(−) 0/21	No recurrence in eighth year
5	48	1 month	2 years	Right RM	(−) 0/20	No recurrence in eighth year
6	62	1 month	1·5 years	Left RM	(−) 0/11	Died in fourth year
7	46	3·5 years	4 years	Left RM	(−) 0/34	No recurrence in sixth year
8	59	8 months	8 months	Left RM	(−) 0/16	No recurrence in fourth year
9	56	14 months	20 months	Left RM	(−) 0/29	No recurrence in fourth year
10	55	5 months	5 months	Left RM	(−) 0/40	No recurrence in first year

RM, radical mastectomy; RT, radiotherapy

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Table 2 *Patients with Paget's disease with a palpable mass in breast*

Patient no.	Age (years)	Time from first symptom to presentation	Time from first symptom to diagnosis	Treatment	Axillary lymph node metastasis	Postoperative follow-up
1	70	7 years	7 years	Right RM+RT	(+) 4/27	Died of unrelated causes in seventh year
2	52	Same day	0·5 month	Right RM+RT	(+) 5/35	No recurrence in 18th year
3	50	3 months	4 months	Right RM	(−) 0/25	Died of unrelated causes in fifth year
4	60	6 months	20 months	Right RM	(−) 0/13	No recurrence in 15th year
5	60	7 months	9 months	Right RM	(−) 0/26	No recurrence in 14th year
6	34	2 months	7 months	Right RM	(−) 0/41	No recurrence in 12th year
7	42	1 month	1 month	Left RM	(−) 0/29	No recurrence in ninth year
8	61	1·5 months	5 months	Left RM	(−) 0/36	No recurrence in sixth year
9	54	0·5 month	4 months	Right RM	(−) 0/25	No recurrence in second year

RM, radical mastectomy; RT, radiotherapy

Clinical data of the nine patients with a palpable mass in the breast in addition to the nipple lesion on whom radical mastectomy was performed are given in *Table 2*.

Discussion

The incidence of clinical or microscopic presentation of Paget's invasion of the nipple with breast carcinomas varies between 0·7 and 4·3 per cent[2–10]. In this series of 937 patients with breast carcinoma, the incidence was 2·5 per cent.

In ten of the 23 (44 per cent) patients the nipple lesion was the only pathological finding. Other series have shown that Paget's disease is the sole evidence of the underlying breast cancer in 30–67 per cent of similar patients[2,3,5,11]. Not being able to find a palpable mass in the breast does not mean that there is no mass there. Even if there is not a clinically palpable mass, macroscopic foci of carcinoma can be found on examination of the mastectomy specimen. In five of our patients with no clinically palpable mass, macroscopic tumour foci ranging from 0·3 to 1·2 cm were found on examination of the mastectomy specimen.

Paone and Baker have stated that mammography and xerography can help in finding the focus of carcinoma in patients with non-palpable masses[11]. Maier *et al.* have stated that prognosis in patients without a palpable mass in the breast is better than for those with a palpable mass[8]. This is related to the more common occurrence of axillary lymph node metastasis in patients with a clinically palpable mass in the breast.

Nance *et al.*[10] and Paone and Baker[11] claim that, in patients without a palpable mass in the breast, no axillary lymph node metastasis occurs. A better prognosis is therefore expected. These authors also claim that in patients with Paget's disease of the breast without a clinically palpable mass, simple mastectomy is adequate for cure. Ashkiari *et al.*[2] found axillary lymph node metastasis in 13 per cent of the patients without a palpable mass and 65 per cent of the patients with a palpable mass.

In Haagensen's Paget's disease series[5], the 10-year survival in patients without a palpable mass was 81 per cent and 52 per cent in patients with a palpable mass in the breast.

In our series we found two patients with axillary lymph node metastasis among 10 patients without a palpable mass. There were also two with axillary metastasis in the group with palpable masses. One patient without a palpable mass died with disseminated disease in her fourth year after operation. The remaining nine who have been followed up for 1–19 years are alive without any evidence of local recurrence or distant metastasis.

Of the patients with a palpable mass in addition to the nipple lesion on whom radical mastectomy was performed, two died from unrelated causes. The other seven are free of disease. No difference in survival rates is apparent between the two groups.

Paget's disease of the breast is a carcinoma of the breast so the treatment must be the same as for any other type of breast carcinoma because multicentric tumour foci and axillary lymph node metastasis can occur.

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Case report

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Pregnancy in a renal transplant recipient complicated by rupture of a transplant renal artery aneurysm

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Although death in a renal transplant recipient is often due to uncontrollable factors, this is not always true. This report deals with a life-threatening condition for which effective treatment is available if the diagnosis is made sufficiently early. The rarity of transplant renal artery aneurysm rupture should not dissuade us from advising ultrasound examination of the graft and vessels at the time of routine obstetric ultrasound examination in pregnant transplant recipients.

Case report

The patient became pregnant for the first time at the age of 20 years. Progress was satisfactory with no abnormality on routine ultrasonography until 32 weeks when she was admitted to the obstetric unit because of postcoital back and suprapubic pain. Physical examination was unremarkable. Cardiotocography, fetal breathing tests and ultrasonography were normal. Blood pressure was 130/90 mmHg and serum creatinine was 90 μmol/l without abnormal protein in the urine. After 6 days observation she was allowed home, only to be readmitted 2 weeks later because of a 2·5 kg weight gain and mild proteinuria. Her blood pressure was 130/80 mmHg. Fetal blood flow by Doppler ultrasonography and fetal heart sounds were normal. Serum creatinine was 85 μmol/l. A putative mild toxaemia of pregnancy was treated by bed rest; 3 days after admission she became suddenly hypotensive and collapsed.

At emergency caesarian section a large amount of blood was evacuated from the peritoneal cavity and a dead infant was delivered. As extensive bleeding seemed to come from the region of the transplanted kidney, the aorta was temporarily compressed which allowed reasonable control of the haemorrhage while vascular surgical assistance was obtained. A ruptured aneurysm of a pelvic artery was recognized and further dissection revealed that this arose either from the internal iliac or renal artery near the site of the anastomosis between these two vessels or from the anastomosis itself. It was not possible to identify which. The aneurysm sac was mobilized and the artery clamped proximally and distally. After excision of the aneurysm, an end-to-end anastomosis was performed between the residual internal iliac and graft renal arteries and the site was marked with a Ligaclip (Ethicon Ltd., Edinburgh, UK). The patient returned home 9 days later. A marginal rise in serum creatinine did not exceed the upper limit of the normal range. Angiography was performed 3 months after surgery to exclude other arterial abnormalities of the transplant renal artery. None was found (*Figure 1*). Eight months after operation the patient remains well with a serum creatinine of 90 μmol/l.

Discussion

Rupture of a mycotic aneurysm of a transplant renal artery is well recognized[1,2] but non-mycotic aneurysms are rare[3–5]. In this patient the aneurysm may have arisen in the graft renal artery, in the native internal iliac artery or from the anastomosis itself. Over 50 per cent of ruptured aneurysms in women under the age of 40 years are related to pregnancy, the most common sites being the cerebral circulation, abdominal aorta and splenic artery[6]. Eighteen cases of native renal artery aneurysm rupture during pregnancy have been reported in the English language literature and 94 per cent occurred in the third trimester with an overall mortality of 56 per cent for the mother and 82 per cent for the fetus[7]. Between 1967 and 1982 there were 24 maternal deaths in England and Wales due to rupture of intra-abdominal visceral arterial aneurysms[8] (ten splenic artery, ten abdominal aortic, three renal artery and one hepatic artery aneurysm). Most ruptures occurred in the last weeks of pregnancy.

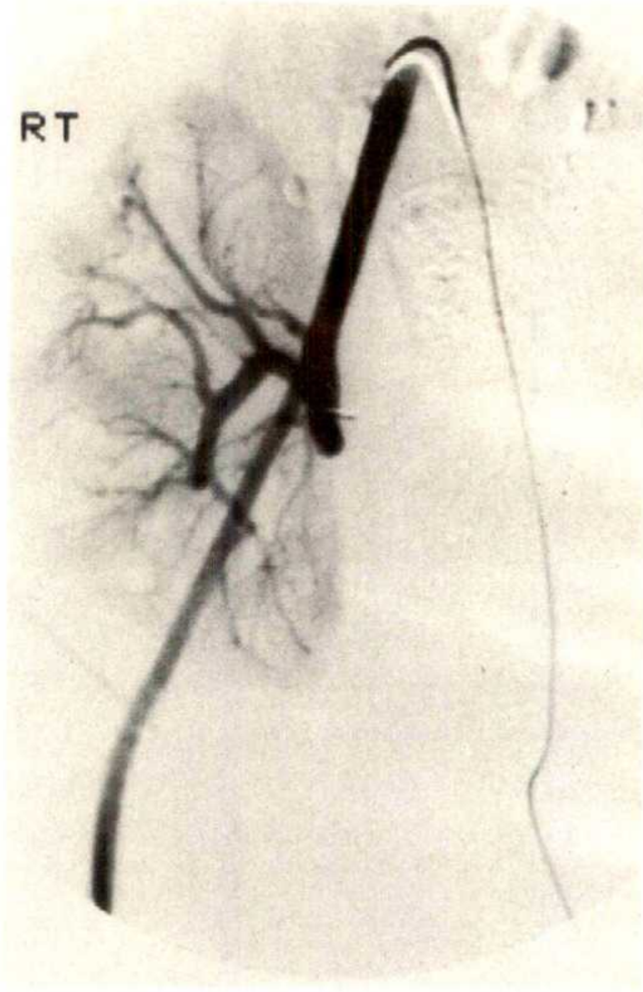

Figure 1 *Angiogram 3 months after surgery: site of aneurysm repair is marked with a Ligaclip*

The mechanism of aneurysm development and rupture is unclear. Experimental evidence suggests that oestrogen may cause intimal hyperplasia and alteration and collagen deposition, predisposing to aneurysm formation[9,10], and increases in circulating blood volume and regional blood flow may predispose to arterial dilatation[6]. Pregnancy may cause intimal hyperplasia and medial structural alteration which is histologically similar to that associated with hypertension[10–12]. The renal artery in the pregnant rat undergoes changes in vessel structure which may become more marked after the third pregnancy[13]. This change is similar to that of fibromuscular dysplasia, which may lead to renal artery stenosis and post-stenotic aneurysm[14]. Only two of the 18 pregnancy-related ruptures of native renal artery aneurysms have been related to this condition[7] and in the present case there was no evidence of renal artery stenosis.

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We report what we believe to be the first case of a transplant renal artery aneurysm rupture occurring in pregnancy. This diagnosis should be considered in any pregnant renal transplant recipient who develops circulatory collapse with abdominal pain. More extensive pelvic ultrasonography in such pregnant patients may be indicated.

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Repeat hepatic resections for colorectal metastases

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We identified 106 patients who had undergone complete resection of isolated colorectal hepatic metastases. Nine of these patients subsequently underwent repeat liver resections for isolated hepatic recurrences. The median follow-up for these patients was 21 months. One postoperative death was related to the second hepatectomy. At the time of last follow-up, five patients were alive and free of recurrent disease at 9, 19, 31, 50, and 67 months after their second hepatic resection. The remaining three patients were alive, but disease had recurred 11 months after resection in the first patient, 12 months after resection in the second, and 18 months after resection in the third. Among these three patients, two had solitary pulmonary nodules, which were resected, and one had unresectable liver disease. Our experience and a review of the literature suggest that repeat hepatic resection for isolated colorectal metastases can result in long-term survival in selected patients. (SURGERY 1990;107:101-4.)

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OVER THE PAST 20 years, many reports have documented that surgical resection of isolated hepatic metastases from colorectal carcinoma can result in a 25% to 30% 5-year survival benefit.[1-13] Relative contraindications for hepatic resection include the presence of positive hepatic nodes, extrahepatic metastases, or four or more liver metastases.[12] As this therapy has gained acceptance, the question of appropriate therapy for recurrent hepatic metastases has become relevant. We present our experience with hepatic resection along with an overview of the few anecdotal case reports to be found in the literature.

RESULTS

Between 1970 and 1987, 106 patients had undergone resection of colorectal liver metastases at the National Cancer Institute (84 patients) or Emory University School of Medicine (22 patients). Among these patients, 9 had a second hepatic resection of recurrent liver metastases (7 at NCI, 2 at Emory). Median follow-up for these patients was 21 months (range, 9 to 67) from the time of the second liver resection.

A summary of these nine cases is compiled in Table I. The median patient age at follow-up was 57 years (range, 44 to 70 years). There were six men and three women. At the first hepatic resection, eight patients had wedge resections and one patient had a right trisegmentectomy for removal of metastatic lesions. Wedge resections were classified as operations that entailed the removal of less than a major lobe. Seven patients had solitary metastases, while patients 3 and 5 had bilobar metastases. Patients 3 through 9 had documented negative resection margins; the status of resection margins for patients 1 and 2 is unknown. In six of nine patients, hepatic resections were performed at the time of primary tumor excisions. The remaining three patients had resection of metachronous liver tumors, which were all diagnosed by elevations in carcinoembryonic antigen levels. Patient 2 received adjuvant systemic fluorouracil chemotherapy after the first hepatic resection.

The median interval from the time of the first hepatic resection to the diagnosis of the hepatic recurrence was 21 months (range, 1 to 39 months). Recurrent disease was initially diagnosed on the basis of elevations in carcinoembryonic antigen levels in six patients and computed tomography (CT) scans in the other three patients. Preoperative evaluation to exclude extrahe-

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Table I. Summary of patients who had second hepatic resections for colorectal metastases

			First hepatic resection†			*Second hepatic resection‡*				
Patient	*Age Sex*	*Primary tumor* Location/Stage*	*DFI (mo)*	*Nodules*	*Operation*	*DFI (mo)*	*Nodules*	*Operation*	*Adj.*	*Follow-up§*
1	56 M	Sigmoid/B2	18	1	R wedge	3	5	R lobectomy	+‖	NED, 67 mo
2	63 M	Sigmoid/C2	0	1	R wedge	33	4	R lobectomy	+	NED, 50 mo
3	57 M	Rectal/C2	0	3	R wedge (2) L wedge (1)	37	1	L lobectomy	+	NED, 25 mo¶
4	67 F	R colon/B2	0	1	L wedge	25	1	R trisegmentectomy	+	Died, 4th postop day
5	62 F	Sigmoid/B2	0	2	R + L wedge	39	1	R lobectomy	+	NED, 31 mo
6	70 M	Rectal/C2	0	1	L wedge	19	1	R wedge	+	AWD, 16 mo
7	44 M	Rectal/C2	0	1	R wedge	1	1	R lobectomy	−	NED, 21 mo¶
8	59 M	Sigmoid/C2 Rectum/C2#	18	1	L wedge	8	1	R wedge	−	NED, 9 mo
9	53 F	Sigmoid/B2	34	1	R trisegmentectomy	21	1	L wedge	−	NED, 19 mo

*Site and locoregional stage of primary tumor (Astler and Coller classification system).
†Data for first hepatic resection include disease-free interval (DFI), documented in months from time of resection of primary tumor to diagnosis of hepatic metastasis (synchronous = 0), and number of nodules resected and type of operation.
‡Data for second hepatic resection include disease-free interval (DFI), documented in months from time of first hepatic resection to diagnosis of second hepatic metastasis, number of nodules resected, type of operation, and adjuvant therapy (Adj) after second hepatic resection.
§Follow-up status in months from second hepatic resection. NED, no evidence of disease; AWD, alive with disease.
‖Plus sign (+) represents administration of adjuvant intraperitoneal fluorouracil therapy.
¶Resection of solitary pulmonary metastasis 11 and 18 months from second hepatic resection in patients 3 and 7, respectively.
#Sigmoid lesion was initially resected and patient was found to have a metachronous rectal tumor.

patic metastases included barium studies of the large bowel, CT scans of the chest and abdomen, and a bone scan. Intraoperative abdominal exploration involved careful palpation and biopsies of hepatic lymph nodes that were found to be clincally suspicious. Seven patients had solitary nodules, while each of the remaining patients had four or five tumor nodules. Second hepatic resections included five lobectomies, one trisegmentectomy, and three wedge resections. Hepatic resection margins for these procedures were all documented to be negative. The one postoperative death involved patient 4, who died of a myocardial infarction occurring on the fourth postoperative day. Five patients were alive and free of disease at 9, 19, 31, 50, and 67 months after the second liver resection. Six patients were given adjuvant intraperitoneal fluorouracil therapy via a Tenckhoff catheter, as previously described.[4] The median survival for all patients was 21 months.

At the end of the follow-up period, three patients had experienced recurrence of disease. Patients 3 and 7 developed solitary pulmonary nodules 11 and 18 months, respectively, after the second hepatic resection. These patients underwent pulmonary metastasectomies and were still alive without recurrent disease 14 and 3 months, respectively, after these procedures. Patient 6 had unresectable disease of the liver 12 months after the second hepatectomy and remained alive with disease at the time of his last follow-up.

DISCUSSION

It is estimated that approximately 10% of all patients with hepatic metastases from colorectal cancer may benefit from liver resection since their recurrent disease is confined to the liver.[14] The Registry of Hepatic Metastases reported a collected series of 859 patients who had undergone resection of colorectal liver metastases. These patients, it was discovered, had a 5-year survival rate of 33%.[12] In a follow-up study reported by the Registry, the site of recurrence in those patients who had complete resection of liver metastases was examined.[15] The liver was the most common site, with 28% of the patients having recurrences limited to the liver and 11% having recurrences in the liver plus other sites. Among our series of nine patients undergoing second hepatic resections, seven patients were documented to have negative pathologic margins at the time of the first hepatectomy, while in the remaining two patients the status of the surgical margins were undetermined. Therefore, it is unlikely that the subsequent recurrences of disease in the liver were related to inadequate first hepatic resections. More likely, the later hepatic recurrences were due to occult liver tumors that were not

Table II. Summary of reported cases of second hepatic resection for colorectal cancer

Author	*No. patients*	*First procedure*	*Second procedure*	*Follow-up**
Nordlinger et al.[11]	6	Wedge resection	R trisegmentectomy	Dead at 25 mo
		Wedge resection	R trisegmentectomy	AWD at 23 mo
		Wedge resection	R trisegmentectomy	NED at 17 mo
		Wedge resection	R lobectomy	NED at 42 mo
		Wedge resection	R lobectomy	AWD at 41 mo
		Wedge resection	Wedge resection	NED at 40 mo
Butler et al.[6]	2	Wedge resection	Lobectomy	NED at 6 mo
		Wedge resection	Lobectomy	NED at 17 mo
Tomas-de la Vega et al.[9]	4	Not reported	Not reported	AWD (2), NED (2); mean survival rate = 22 mo
Fortner[20]	3	Lobectomy	Wedge resection	AWD at 39 mo†
		Lobectomy	Wedge resection	Alive at 5+ mo‡
		Lobectomy	Wedge resection	Dead at 16 mo

*Follow-up status in months from second hepatic resection. NED, No evidence of disease; AWD, alive with disease.
†Recurrent disease in lung and pelvis documented 7 months after second liver resection. Had four subsequent operations for localized recurrent disease.
‡Had a second recurrence of the disease in the liver and underwent third liver resection. Alive 5 months after last liver resection.

detected at the time of the first hepatic resections. The increasing use of intraoperative ultrasound may improve the ability of the surgeon to detect occult lesions not identified by CT scanning or manual palpation at the time of surgery, and it may also aid in achieving adequate surgical margins.[16]

Data from the literature and our experience suggest that approximately one third of all isolated liver metastases are technically resectable. In the past, the major deterrent to aggressive metastasectomies of the liver has been the associated morbidity and mortality. Increased blood loss and transfusion requirements have been reported to increase postoperative complications and decrease disease-free and overall survival after liver resections.[4, 17] Advances in hepatic parenchymal dissection and diagnostic evaluation of colorectal cancer also offer promise for improving the feasibility of hepatic metastasectomies. The Cavitron ultrasonic surgical aspirator (CUSA) has been reported to provide a more controlled dissection of the hepatic parenchyma with better identification of vasculobiliary structures and decrease operative blood loss, compared with conventional techniques.[18] Careful monitoring of carcinoembryonic antigens can lead to the earlier detection of recurrent liver tumor that may be more amenable to surgical resection.[19] Likewise, newer diagnostic scanning techniques have improved the sensitivity and resolution of diagnosing smaller hepatic nodules.

Our study encompasses the largest reported series of patients who have undergone second liver resections for colorectal metastases. Four other reports have commented on a total of 15 patients who have had repeat liver resections for metastases.[6, 9, 11, 20] A summary of these other cases is listed in Table II. Seven of these 15 patients remained alive and free of disease at the time of follow-up 6 to 42 months after their second hepatic resection. Among the nine patients reviewed in our series, two have remained free of disease for more than 4 years, longer than any patient in the previous reports. Combining the data on all the patients with individual follow-up information from our series and others, we concluded that the median survival time for patients after their second liver resection was 22 months (n = 20).

The events leading to the growth and development of metastatic disease in lymph nodes or visceral organs are complex and poorly understood.[21] Surgical resection of metastatic disease has been a therapeutic option that has been traditionally dismissed by clinicians as being curative. However, it should be reiterated that surgical resection of regional lymphatic metastases from solid tumors such as melanoma and colorectal and breast carcinomas can be curative in 25% to 40% of patients.[22] For blood-borne visceral metastases, extensive clinical experience has documented that resection of isolated pulmonary and hepatic tumors can result in 25% to 30% long-term survival.[1-13, 23] The ability to cure a select group of patients with metastatic disease involving the lymph nodes or visceral organs by surgical means alone suggests that the number of residual micrometastatic tumor cells can be reduced to a level capable of being destroyed or suppressed by host mechanisms.

The therapeutic benefits of reoperation for recurrent metastases in the lung have been documented. Rizzoni et al.[24] reported on the National Cancer Institute (NCI) experience of repeat pulmonary resections for soft-tissue sarcoma lung metastases which resulted in prolonged survival.[24] Twenty-nine patients who had two or more pulmonary resections had a median survival of 14.5 months, with a 3-year survival of 22%. No major operative morbidity was associated with repeat pulmonary resections. The biologic principles that allowed for prolonged survival after reoperation for recurrent metastases in the lung may also be valid in the case of repeat hepatic resections of colorectal metastases. The technical problems of performing repeat pulmonary resections (up to four in the NCI experience) are clearly less than for repeat hepatic resections. However, the unique ability of the liver to regenerate may make a second liver resection more feasible. For example, patient 9 underwent an initial right trisegmentectomy for a 4 cm metastasis within the medial segments of the right and left lobes; 21 months later, the patient was able to undergo a large wedge resection of a 5 cm solitary metastasis in the residual left lobe, which had exhibited marked regeneration.

In our series, six patients received adjuvant intraperitoneal fluorouracil after the second hepatic resection (Table I); however, the role of adjuvant chemotherapy in patients surgically rendered free of metastatic disease in the liver has yet to be established. Effective adjuvant treatment after liver metastasectomies is an important area for future investigation. The cases presented here, as well as a review of the literature, suggest that aggressive repeat resection of recurrent colorectal metastases confined to the liver may be beneficial in selected patients.

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Correspondence

Typhoid perforations

Sir

We read with interest the article on typhoid perforations by Gibney[1]. While listing the various procedures for operative treatment, mention of tube ileostomy in the treatment is omitted. This was originally described by Lusoya[2].

We agree that all typhoid perforations must be managed operatively after resuscitation. However, in view of the severity of contamination and marked bowel distension due to ileus there is danger of reperforation or fresh perforation if adequate decompression is not achieved. To this end we have advocated a tube ileostomy through the perforation using a 24 Fr Foley catheter. In case of multiple perforations it is put via the most proximal perforation and the rest closed in two layers using Vicryl® (Ethicon Limited, Edinburgh, UK) and silk. The tube is removed after 2 weeks.

In patients with severe contamination and grossly distended bowel we perform laparostomy and repeat peritoneal toilet is done after 48 and 96 h. At this time any collections can be evacuated. It is also possible to identify re- or fresh perforations and treat them. This procedure markedly reduces intra abdominal abscess formation and delayed mortality.

During the period 1978–85, 71 cases of typhoid perforations were treated. The treatment undertaken and mortality respectively were: simple closure, 30; resection and anastomosis, 6; resection and ileotransverse colostomy, 5; and tube ileostomy, 28. Two cases were treated conservatively and both died.

Consequently, since 1985 we have adopted tube ileostomy as standard treatment with selective laparostomy. A further 27 cases have been thus treated and laparostomy done in nine cases. Postoperative mortality numbered 2 (7·4 per cent). Both patients presented more than 72 h after perforation and mortality is related to septicaemia and delay in treatment.

Enterocutaneous fistula is a major complication in these patients with five instances in the simple closure group and two in the resection anastomosis group. No patient in the tube ileostomy group developed fistula. There was no significant leak after removal of the tube. The mortality rate is comparable to those in other series and is among the best in literature. Eggleston[3] reported a 32 per cent mortality rate using resection and anastomosis or ileotransverse colostomy. Meier[4] reports a 32 per cent mortality rate using debridement and closure.

Therefore it is our contention that tube ileostomy has a definite role in the treatment of typhoid perforations. The procedure is simple, safe and associated with low mortality and morbidity.

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Cholecystokinin provocation test

Sir

The cholecystokinin (CCK) provocation test and long term follow-up after cholecystectomy was reported in this journal by Rhodes *et al.* (*Br J Surg* 1988; **75**: 951–3). This study prompted us to review our own experience with the CCK provocation test in a group of 40 patients who satisfied the criteria for the diagnosis of acalculous biliary disease, i.e. (right upper quadrant pain suggestive of biliary origin, negative oral cholecystogram, ultrasound, barium meal and/or oesophagogastroscopy).

In this series there were 14 positive tests, all of whom underwent cholecystectomy with complete resolution of symptoms in 13 cases. Seven cases underwent repeat testing 6 weeks after surgery, and in each of these cases the CCK test had become negative. Histology of the resected gallbladders showed eight cases of chronic cholecystitis, three cases of cholesterolosis, and three histologically normal gallbladders. Of the 26 cases with negative tests, 14 experienced spontaneous resolution of symptoms, eight remain symptomatic and four had an alternative diagnosis made.

Sunderland and Carter[1], in a comprehensive review of the subject, suggested that there is no place for the CCK test in the investigation of those patients thought to have acalculous biliary pain. They cite a failure to show a difference in outcome from studies in which both CCK positive and negative patients have had an operation[2]. They further quote the study of Byrne *et al.*[3], who showed no difference in outcome between a group of 48 CCK positive patients who had cholecystectomy and conservative management.

Valid criticisms are that the test as originally advocated does not allow for the placebo effect of cholecystectomy, and that there is no pathological material available for comparison in the CCK negative groups. Placebo effect, however, cannot explain the conversion of the seven individuals with positive tests who became negative when tested 6 weeks after surgery. In these cases, it would seem that a 'dysfunctional' target organ was removed. In our experience a positive CCK provocation test convincingly reproduces the patients' original biliary type right upper quadrant pain. A false positive test is characterized by diffuse abdominal pain with associated nausea and retching. It is difficult to refute the arguments of Sunderland and Carter with regard to the discriminatory power of the test. However it would appear from our own study that patients with a positive CCK test have an excellent chance of symptomatic improvement following cholecystectomy. To abandon further investigation into the mode of action of an agent which so convincingly appears to reproduce the symptoms of acalculous biliary pain would seem ill advised.

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Selection of patients for breast conservation

Sir

May I congratulate Mr A. E. Young on his balanced leading article (*Br J Surg* 1989; **76**: 885) which emphasizes some points previously made in a letter to the Annals (*Ann R Coll Surg Engl* 1988; **70**: 57). His article came as a breath of fresh air to the silent majority of Surgeons who are neither unflinching mastectomists or conservationists.

Encouraged by some specialists, the mass media have told our patients that mastectomy is no longer necessary; they have not been told that if this policy was widely adopted, there would be an increased local recurrence rate with difficulties in its detection and management. There has been no mention of the short and long term side effects of radiotherapy, the dissatisfaction of some ladies having had this treatment and the possible (as yet unknown) effect on mortality.

I hope this article will help redress the balance.

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Transanal resection of rectal tumours

Sir

Due to urinary bladder and rectal ampoule similarity, the conventional urological transurethral resector instrument has been used to resect tumours of the rectum in nine patients. The technique being used in our unit is to routinely prepare the colon as for a resection, and with an epidural anaesthetic and the routine antibiotic cover, the patient is placed in the lithotomy position and a Foley catheter is passed through the anus and anchored by the balloon at the rectosigmoid junction. This enables the rectum to be closed and irrigated with a solution of glycine. A double channel resectoscope is used with an optic of 30° and diathermy is used for cutting the tumour. In the female the level of resection can be guided by a finger in the vagina.

We have resected three patients with adenocarcinoma of the rectum with good results. The pain, tenesmus and bleeding all resolved and normal bowel function returned. Of six patients with multiple polypoid disease, the polyps were controlled in five patients; however, a rectal excision was necessary in the sixth patient because of relapse of the villous tumour. We have found this technique especially useful when treating rectal villous adenoma in the sessile form as it is easier to control the level of resection with a diathermy and electrocoagulation than conventional techniques. Further, good samples are achieved for histological analysis.

We have also used the technique in recurrent polyps in two patients and multiple polyps in one patient because of the ease with which the resection can be repeated with miminum risk[1,2].

There has been no significant morbidity in any patient and the hospitalization period has been short. Because of the frequency of rectal tumours, this endoscopic approach has proved useful involving little risk to the patient with only minimum chance of perforation of the extraperitoneal rectum and even if this does occur it is not necessarily clinically apparent[3,4].

Based on our experience we would recommend that this technique of endoscopic resection is indicated firstly in polypoid disease of a sessile nature, and secondly for malignant tumours of the rectum which are unsuitable for resection, such as patients with metastatic disease and in those who have a poor prognosis on account of age or other disease.

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Doppler flowmetry *versus* on-table angiography

Sir

We enjoyed the paper by Beard *et al.* (*Br J Surg* 1989; **76**: 925–8) concerning their elegant use of Doppler flowmetry to predict early graft failure in femorodistal bypass. We feel, however, that some of the technical problems unmasked by the flowmeter could have been avoided by employing on-table angiography before grafting. These include the two patients who required distal graft extensions to bypass disease at the tibial vessel origins and the patients in whom postgrafting angiography revealed severe distal disease. Presumably these stenoses were not seen on preoperative angiograms. The increased sensitivity of on-table angiography in localizing calf vessel disease[1] allows optimal placement of the distal anastomosis. We routinely use on-table angiography to complement preoperative Doppler assessment[2] and have found it reliable and simple to perform. It commonly reveals trifurcation and distal stenoses that were not seen on preoperative angiograms (when performed).

It is possible that Doppler flowmetry represents an improvement on our current technique of operative graft assessment. This involves electromagnetic flowmetry and the appearance of the revascularized foot followed, if problems are revealed, by completion angiography. We suspect, however, that Doppler flowmetry takes longer and is more difficult to perform. This may prevent its use outside research centres.

We agree that peripheral resistance is likely to be the most important parameter in the prediction of early graft failure. We have found by duplex scanning of femorocrural grafts that in the most severely ischaemic limbs the postoperative pulse waveform is narrow and indicative of a high peripheral resistance. The waveform gradually broadens over 48–72 h and is associated with an increased systolic velocity and improved graft flow. This 'low-reflow' phenomenon may be due to ischaemic damage to the capillary endothelium with subsequent cell swelling, a narrowed lumen and secondary plugging with leucocytes[3]. It is likely that this phase of high peripheral resistance and low graft flow is a critical period with respect to graft patency. We are currently investigating the pharmacological manipulation of peripheral resistance and graft flow with the prostacyclin derivative iloprost.

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1. Scarpato R, Gembarowicz R, Farber S *et al.* Intraoperative pre-reconstruction angiogrphy. *Arch Surg* 1981; **116**: 1053–5.
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Author's reply

Sir

In their letter, Mr Simms *et al.* extolled the virtues of on-table angiography before femoropopliteal bypass grafting. The problem with any form of arteriography is that it gives a uniplanar view and therefore the severity of any stenosis may be over or under estimated. Neither does it provide any information about the functional capacity of the distal run-off. We accept that on-table arteriography often gives better definition than conventional preoperative arteriography but the same limitations still apply.

We do not rely on preoperative arteriography to define the distal vessels but use the Pulse Generated Run-off system recently described in *The British Journal of Surgery*[1]. Most of the technical problems demonstrated by Doppler flow measurements could not have been avoided by on-table angiography before grafting as they were related to the graft or anastomoses. We feel that functional assessment of the distal run-off by measuring the peripheral resistance is desirable and more physiological than arteriography alone. Measurement of blood flow and peripheral resistance, using the new Doppler flow meter, is much easier and quicker than using electromagnetic flow meters which are unreliable and difficult to calibrate. The Doppler flow meter should certainly not be limited to research centres. It has been designed for use by any vascular surgeon without requiring technical support.

We would agree that it is not uncommon to find relatively high peripheral resistance following grafting of ischaemic limbs and are also investigating pharmacological manipulation of peripheral resistance to try and improve graft patency.

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1. Beard JD, Scott DJA, Evans JM, Skidmore R, Horrocks M. Pulse-generated runoff: a new method of determining calf vessel patency. *Br J Surg* 1988; **75**: 361–3.

Book reviews

Scott: An Aid to Clinical Surgery. 4th ed.

H. A. F. Dudley, B. P. Waxman. 245 × 185 mm. Pp. 315. Illustrated. 1989. Edinburgh: Churchill Livingstone. £9.95.

The authors begin by outlining three aims for a book clearly aimed at undergraduates. Firstly, it should provide the student with enough facts and vocabulary to make them feel at ease on a surgical ward; secondly, it will give them sufficient information to pass their examinations and finally, it will introduce them to solving clinical problems. Whilst I am confident that they have achieved the first two, I remain unconvinced about the last.

Duplication is minimal. Figures are mostly line drawings of acceptable quality, with radiology featuring only in the CNS. Nevertheless, for a book in its fourth edition, there were still some unfortunate errors. The figure purporting to show a Polya gastrectomy without a Hofmeister value clearly depicts one, and the omission of the letters 'in . . . ' makes nonsense of the sentence that 'sufficient intrinsic factor leads to a macrocytic anaemia after gastric surgery'.

In any text covering a wide field, there are bound to be sources of irritation to any surgical teacher, whether these are of nomenclature (multiple endocrine adenomas really should be multiple endocrine neoplasia), the use of neologisms such as cholegram and prostatomegaly, or just plain disagreement (I know that I am not the only surgeon who regularly uses cytology to make a diagnostic decision about breast cancer).

To the authors' credit, though, I found this book easy to read and it is succinct. The important thing for any medical student is to find a text that appeals to that individual, and I am sure that this book will be attractive to some.

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Surgery of the Liver

M. V. McDermott. 285 × 225 mm. Pp. 560. Illustrated. 1989. Cambridge: Blackwell Scientific. £95.00.

Although 43 'leading authorities on the liver' have compiled this book, 31 of these are based in Boston and there are only four non-American contributions. Each of the chapters is followed by an Editorial comment, testifying to the high quality of each contribution. Nonetheless, the standard is variable and is well-illustrated by the first chapter in the section relating to basic science. The visceral relationships of the liver are discussed in this unreferenced section on surgical anatomy but there is scant mention of intrahepatic anatomy or vascular anomalies. The inclusion of the liver's segmental anatomy in the Editorial 'vignette' at the end of this chapter does not prevent the book from starting off on the wrong foot. A clear and concise review of liver function tests over 12 pages has been supplemented unnecessarily with an overly long 23 page chapter on the role of amino acid clearance in assessing liver disease. Subsequent chapters in this section and the section on assessment and diagnosis are well referenced and up-to-date. It was disappointing, however, to see no mention of the role of intraoperative ultrasonography in hepatic resection.

The strength of this book lies in the Editor's own field of interest, namely in the section on medical and surgical treatment of variceal haemorrhage. However, it was surprising to see a chapter on elective portasystemic shunts restricted in an American textbook to only seven pages. The quality of the figures and diagrams is variable throughout the text, and the chapter on hepatic trauma has no illustrations. The chapter on liver resection is poorly presented and contains no description of segmental resections. Whilst the reader may find parts of this book a useful source of reference, I suspect that the Editor will have difficulty competing with other established textbooks in the field.

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Essential Urology

N. Bullock, G. Sibley, R. Whitaker. 235 × 155 mm. Pp. 416. Illustrated. 1989. Edinburgh: Churchill Livingstone. £9.95.

Although this book makes no attempt to produce a comprehensive catalogue of all known urological disorders, it provides a carefully thought out and well balanced review of contemporary urology incorporating both basic principles and recent developments in the field. The book starts with a review of the structure and function of the urinary tract followed by sections on urological history, examination and the investigation of urological symptoms. It is particularly gratifying to see a text book which simply summarizes in an understandable format the role and importance of urodynamics in the functional investigation of the urinary tract and its importance to the practice of 'modern' urology. This theme is developed in the individual sections demonstrating the application and importance of these techniques to the investigation of obstruction, incontinence and bladder disorders resulting from neuropathy. The book also contains sections on urinary tract trauma, infection, urinary calculi, haematuria, urinary tract tumours and disorders of the penis and scrotum. In addition more specialized topics are covered, including: renal failure, dialysis and transplantation, renal and adrenal hypertension, sexually transmitted disorders and male infertility. Congenital anomalies of the upper urinary tract are succinctly reviewed including the difficult subject of intersex and a useful section on the investigation and treatment of a child presenting with urinary infection.

An appealing feature of this book is the clarity with which information is presented. Although it is inevitable in a book of this size that many of the comments are necessarily brief, the authors have managed to provide a comprehensive general overview of the subject. The text is extensively illustrated with tables and diagrams which complement the written word. I have no hesitation in recommending this work as a definitive basic text book on contemporary urological practice which provides a useful review of this subject and should also be of value to the surgical trainee.

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Rob & Smith's Operative Surgery, 4th Ed. Paediatric Surgery.

L. Spitz and H. H. Nixon. 285 × 220 mm. Pp. 703. Illustrated. 1988. London: Butterworths. £160.00.

Although Operative Surgery is now in its fourth edition, the section specifically devoted to Paediatric Surgery is only in its second. This edition is significantly better in the general layout. First because of the uniformity of illustrations, many much improved; and second, almost every section now has a list of references or titles for further reading. Unfortunately some of these simply refer to the author's own work instead of offering a lead to finding other techniques.

The book commences with sections on neonatal transfer, physiology and anaesthesia which are most welcome, particularly commendable is the section on physiology. It is unfortunate that no section was included on the Paediatric Surgeon's role in antenatal diagnosis and counselling.

A major difficulty for Editors of such a book is to define boundaries for the subject. Some specialty overlap such as the excellently illustrated section on hare-lip and cleft palate is appropriate. However, in other fields omissions are surprising; for example no mention is made of surgery for encephalocele or craniosynostosis which are often managed by Paediatric Surgeons. It is unfortunate that the section on 'Urinary Diversion, Undiversion' is in a different style.

This new edition of Operative Surgery, Paediatric Surgery is greatly improved and should be available to anyone practising this specialty.

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Management of Oesophageal Carcinoma

R. L. Hurt. 250 × 170 mm. Pp. 298. Illustrated. 1989. London: Springer Verlag. £85.00.

This short book reviews the field of oesophageal cancer. It starts with a historical review which shows how recently the technical problems of resecting the oesophagus have been tackled with any success. Subsequent chapters discuss surgical anatomy, epidemiology, endoscopic and radiological diagnosis. The remarkable regional variation in incidence of these tumours shows that it should be possible to learn something about their cause by epidemiological studies. Unfortunately areas of high incidence tend to be in countries where endoscopy and radiology (including CT and magnetic scanning) are not widely available. The section on pathology, however, shows that we are still some way from identifying specific carcinogens.

Chapters follow on surgical resection at different levels – postcricoid or intrathoracic. Different surgical techniques are fully described. There are good descriptions of operative technique, and of intubation, radiotherapy, and intracavitary radiation, cytotoxic therapy, and laser treatment. The treatment of complications is also extensively discussed.

The generally unsatisfactory results in this distressing condition – a mortality of 10–20 per cent following operations and 5 years survival of only 15–20 per cent – might lead to the conclusion that cases should be referred to specialist units where they would get better treatment than is generally available in our District General Hospitals. Since this idea runs contrary to tradition in the UK perhaps more would be achieved if the book were widely read by those of us who treat the cases which come our way. The cost of the volume (£85.00) cannot be regarded as excessive if even one patient received cure, or palliation, as a result.

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Basic Surgical Techniques

R. M. Kirk. 185 × 120 mm. Pp. 304. Illustrated. 1989. Singapore: Churchill Livingstone. £9.95.

It you are a SHO who has just begun a surgical career then this may be the book you should browse through after your first few weeks in the job. It is not an operation manual but tells you a great deal about some of the very basic surgical manoeuvres which come naturally with time but which are not usually taught by more senior surgeons. It includes chapters on incisions, sutures, dissection and the handling of various types of tissues. It is a book which will be helpful for a short period at the start of training but will be rapidly replaced by the need for more specific operative manuals. Nevertheless this does not make its content less important.

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Year Book in Vascular Surgery

J. J. Bergan, J. S. T. Yao. 235 × 155 mm. Pp. 327. Illustrated. 1989. St Louis: Mosby-Year Book Inc. £42.00.

The Year Book in Vascular Surgery series has, to date, been highly regarded, and this present volume will only serve to enhance the series' reputation. Bergan, Yao and their colleagues have managed to sift the literature of a year for worthy material from sources which are surprisingly catholic, with the result that a genuinely international spread of work is displayed.

A volume like this cannot be easy to compile and certain balances must be achieved. Firstly, there is the balance of 'too little' or 'too much' in the 311 individual expanded abstracts which go to make up the book. Generally, these abstracts are of a size big enough to convey sophisticated messages while remaining short enough to hold the reader's attention. Secondly, there is the balance of subjects to be discussed. The topics cover a wide spread of both arterial and venous disease, and the chapter on vascular trauma is particularly timely and worthy of the attention of all in the vascular surgical field. Finally, there is the balance of laboratory *versus* clinical investigation and it is in this area that the true spirit of the book shines through. Although much of the volume concerns itself with clinical work, there is a satisfactory and satisfying number of laboratory based abstracts which carry clear implications for the practising doctor. Even the dullest and most steam-driven of clinicians should be able to grasp their importance.

In summary, this book has much to offer all who work with patients suffering from peripheral vascular disease. Too many books are described as being 'essential reading' but, for the vascular surgeon, this one really is!

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Progress in Surgery. Volume 3

I. Taylor. 230 × 155 mm. Pp. 320. Illustrated. 1989. Edinburgh: Churchill Livingstone. £17.50.

It was a pleasure to read this third volume of Progress in Surgery which sets out to inform surgical trainees on a broad base and to keep established surgeons abreast of developments outside their special interest.

Immunology for the surgeon does require concentration and the chapters on anorectal problems in children and intracerebral haemorrhage are rather specialized but none of the chapters are lacklustre. I enjoyed the chapter on abdominal trauma and the rather unexpected account on venous access. The chapters on venous thrombosis and chemotherapy for colorectal cancer give a fair and up-to-date account which is just what is needed by the examination candidate.

The Editor is to be congratulated for producing a worthwhile and easily readable volume which is well-suited for the trainee and the consultant. At £17.50 it is modestly priced and should be available in every hospital library.

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Controversies in general surgery

T. G. Allen-Mersh. 235 × 155 mm. Pp. 122. Not illustrated. 1989. London: Edward Arnold. £10.00.

Surgeons are an argumentative bunch. Nothing could be more appealing than the prospect of a bare knuckle fight between the champions of hotly contested causes: 'Surgery without prophylaxis against deep vein thrombosis is negligent'; 'A 50 per cent ulcer relapse rate after one year of H_2 antagonists is preferable to a 10 per cent relapse after proximal vagotomy'; 'Surgery has no place in the management of the symptoms of chronic pancreatitis'; and 'Monitoring of serum CEA after colorectal cancer serves merely to forewarn the patient of his impending demise' – to mention but four of the ten controversies in this 122 page book. The champions were surgeons in the Charing Cross and Westminster surgical training scheme (many of whom are now Consultants).

How is it that clever people can adhere to diametrically opposed opinions on these sorts of issue when they are presented with all the facts? The answers are: they didn't read/assimilate/believe the facts; they have a different set of objectives to each other; and, they don't actually believe what they have argued. As the various authors were allocated their topics and told what their stance was to be the inevitable conclusion in this case must be the third. Nevertheless, the book is enjoyable and contains many useful references. But what fun could have been had were real champions to have shed each other's blood! And what an opportunity that would have been for the rest of us to see real bigotry at work!

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Notices and announcements

4–9 February 1990
HIV and AIDS: Management and Control
London, UK
Information: The British Council, Courses Dept, 65 Davies Street, London W1Y 2AA

19–23 February 1990
Sixth Annual Winter Imaging Seminar: Perspectives in imaging
Cancun, Mexico
Information: Janice Ford, Continuing Education, Dept of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia PA 19104, USA

2 March 1990
Assessment and Care for Patients Undergoing Abdominal Aortic Surgery
Exeter, UK
Information: Mrs L. Graves-Morris, Secretary to Mr W. B. Campbell, Dept of Surgery, Royal Devon & Exeter Hospital, Barrack Road, Exeter EX2 5DW, UK

4–10 March 1990
Cancer in Children
London, UK
Information: The British Council, Courses Department, 65 Davies Street, London W1Y 2AA, UK

11–13 March 1990
2nd Surgical Masterclass of the Royal College of Surgeons of Edinburgh
Aviemore, UK
Information: Mrs Maureen Webb, The Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

15–18 March 1990
2nd World Congress of Surgical Endoscopy, Ultrasound and Interventional Techniques
Atlanta, Georgia, USA
Information: Program Committee, SAGES, World Congress on Surgical Endoscopy, Suite 409, 1271 Stoner Ave, Los Angeles, CA 90025, USA

19 March 1990
One Day Symposium on Endoscopic Equipment
London, UK
Information: Mr R. A. Miller, Consultant Urologist, Whittington Hospital, St Mary's Wing, Highgate Hill, London N19 5NF, UK

19–29 March 1990
Advances in Neurosurgery
Glasgow & Edinburgh, UK
Information: Courses Department, The British Council, 65 Davies St, London W1Y 2AA

28–30 March 1990
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Cardiff, UK
Information: The Honorary Secretary, Association of Surgeons of Great Britain and Ireland, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

1–6 April 1990
Clinical Genetics
Cardiff, UK
Information: British Council Office, Courses Department, 65 Davies St, London W1Y 2AA

2–12 April 1990
The Clinical Medicine of Later Life: the Scientific Basis of Practice
Oxford, UK
Information: The British Council Courses Dept, 65 Davies Street, London W1Y 2AA, UK

27–28 April 1990
The 3rd International Symposium on Gynaecological Endoscopy
Oxford, UK
Information: Metaphor Conferences & Meetings, 21 Kirklees Close, Farsley, Pudsey, West Yorkshire LS28 5TF, UK

2–4 May 1990
17th Biennial Congress of the Association of Surgeons of South Africa in Bloemfontein
Bloemfontein, South Africa
Information: Dr GF Ferreira, Dept of Surgery, (G72) Univ. of the OFS, Box 339, Bloemfontein 9300, Republic of South Africa

9–12 May 1990
3rd International Symposium on Echocardiography and Doppler in Cardiac Surgery
Vienna, Austria
Information: W. Mohl, c/o Interconvention, A-1450 Vienna, Austria, +43/1/23 69/2642

16–18 May 1990
Blood Vessel Imaging Using Ultrasound Techniques
Southampton, UK
Information: Mr K. N. Humphries, Blood Vessel Imaging Course, 10 Swale Drive, Chandlers Ford, Hampshire SO5 3QY, UK

29 May–1 June 1990
Peripheral Vascular Disease
London, UK
Information: The British Council, Courses Department, 65 Davies St, London W1Y 2AA

5–9 June 1990
European Association for Gastroenterology & Endoscopy: European Digestive Disease Week
Vienna, Austria
Information: Mondial Congress, Faulmanngasse 4/11 A-1040 Wien, Austria

8–9 June 1990
3rd Annual Meeting of The Surgical Infection Society
Antwerp, Belgium
Information: Professor A. Hubens, University Dept of Surgery, Stuivenberg General Hospital, Lange Beeldekenstraat 267, B-2008 Antwerp, Belgium

11–14 June 1990
6th International Congress on Breast Diseases
Boston, Massachusetts, USA
Information: 6th International Congress Secretariat, c/o Office of Continuing Education, Tufts University School of Medicine, 136 Harrison Avenue, Box 36, Boston, MA 02111, USA

13–16 June 1990
5th European Symposium on Gastrointestinal Motility
Augsburg, FRG
Information: Professor M. Weinbeck, Dept. of Internal Medicine III, Zentralklinikum, D-8900 Augsburg, FRG

20–23 June 1990
Annual Meeting of The Endocrine Society
Atlanta, Georgia, USA
Information: Ann Singer, Meetings Manager, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

24–28 June 1990
XIII Biennial Meeting of I.S.U.C.R.S.
Graz, Australia
Information: Miss D. Strauss, Executive Secretariat, c/o Indru T. Khubchandani, 1275 S. Cedar Crest Boulevard, Allentown, PA 18103, USA

24–29 June 1990
The 3rd Oxbridge Organ Transplantation Course
Oxford, UK
Information: British Council Office, Courses Department, 65 Davies St, London W1Y 2AA

12–14 July 1990
XVth International Update on Liver Disease
London, UK
Information: Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

14–15 July 1990
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

15–21 July 1990
1990 Surgical Updating
Milan, Italy
Information: Segreteria Organizzativa, MGR, Via Servio Tullio, 4-20123 Milano, Italy

22–27 July 1990
FASEB Summer Research Conference 'Physiology and Pathophysiology of the Sphlanchnic Circulation'
Colorado, USA
Information: Federation of American Societies for Experimental Biology, Splanchnic Circulation Conference, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

22–24 August 1990
International Hepato-Biliary Pancreatic Assoc. 12th Annual Meeting
Hong Kong
Information: The Secretariat, IHBPA Hong Kong, Department of Surgery, Queen Mary Hospital, Hong Kong

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OFFICIAL PUBLICATION OF:
The Society for Surgery of the Alimentary Tract
The North Pacific Surgical Association
The Society for Clinical Vascular Surgery
The Society of Head and Neck Surgeons
The Southwestern Surgical Congress
The Association for Surgical Education

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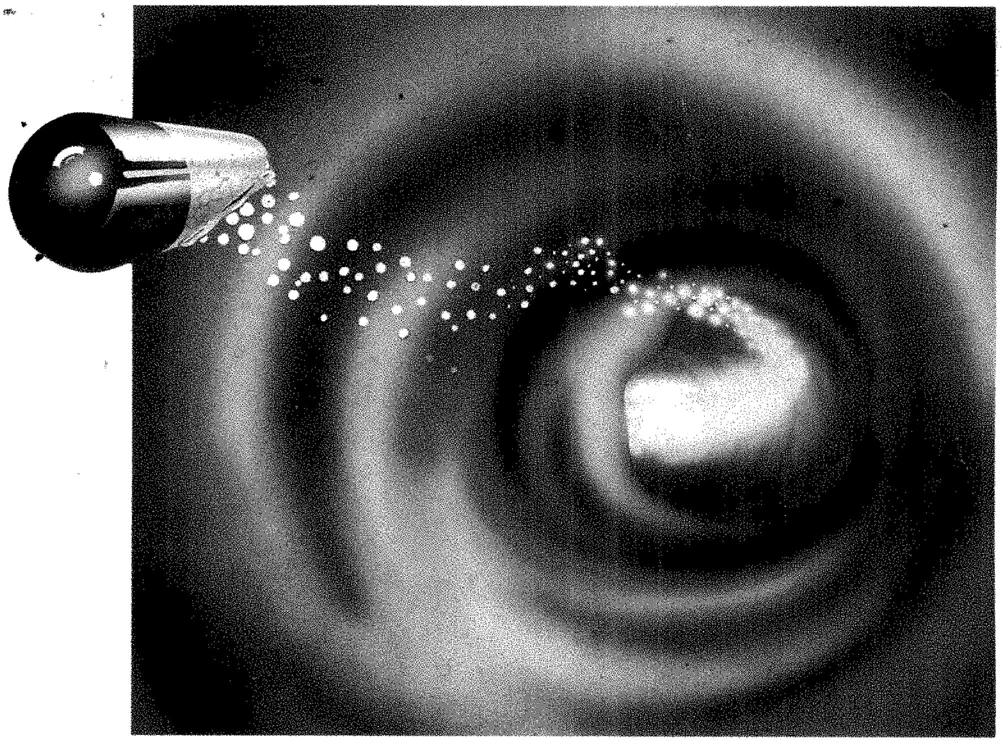

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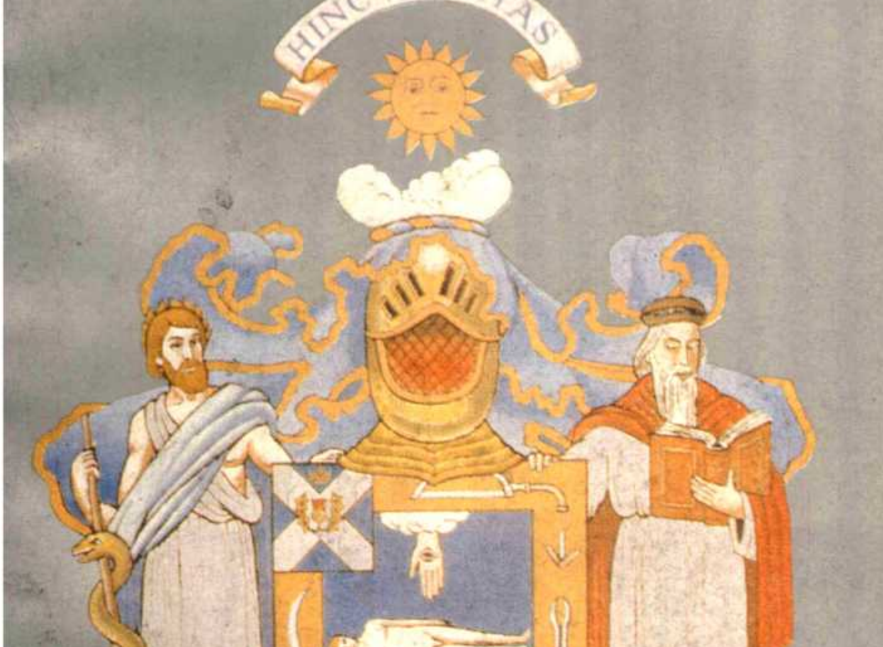

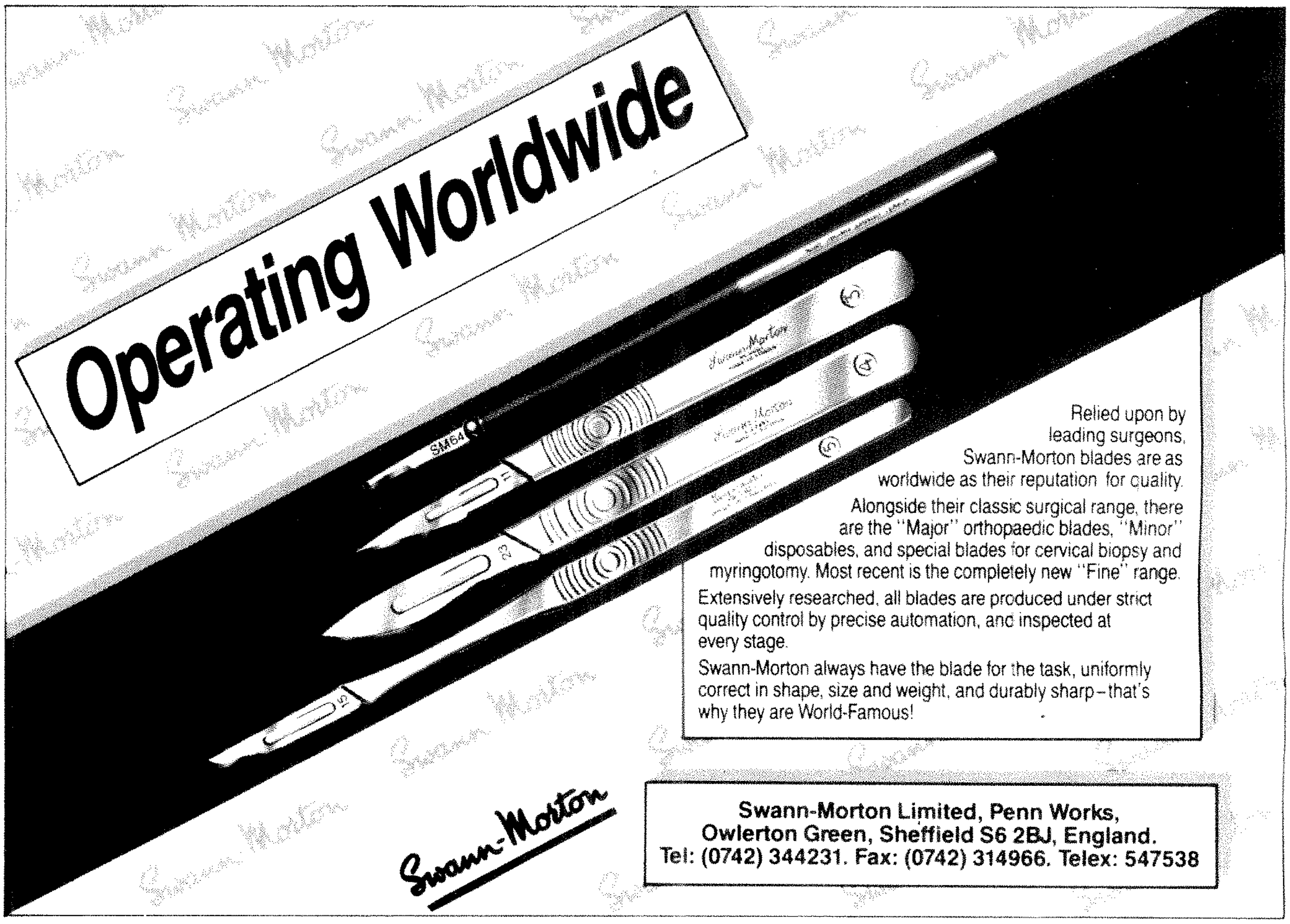

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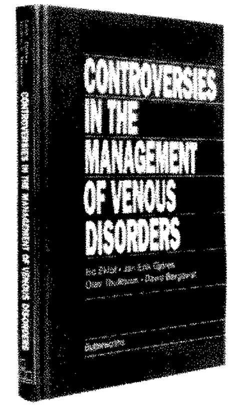

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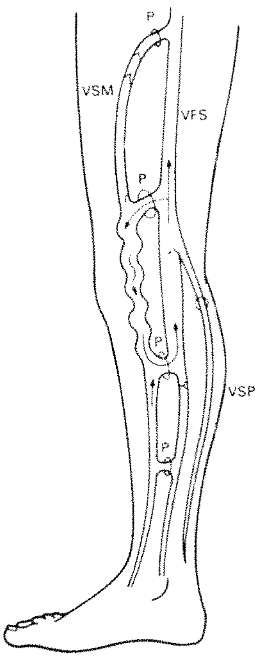

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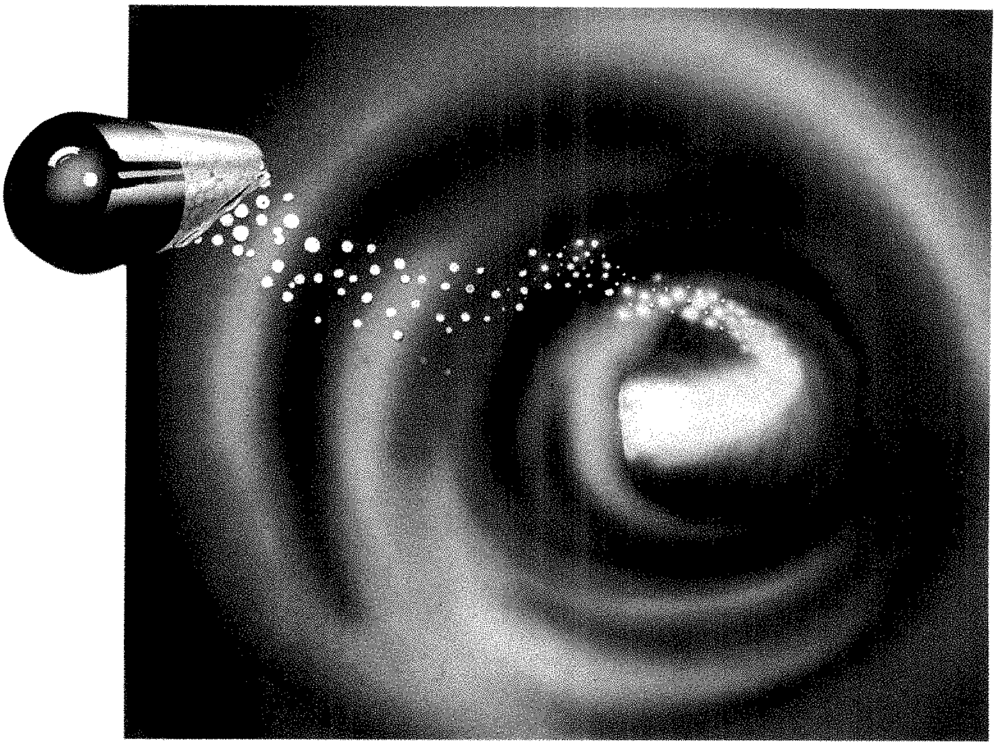

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Br. J. Surg. 1990, Vol. 77, April, 361–362

Early operative fracture management of patients with multiple injuries

Immediate mortality following multiple injury is mainly accounted for by brain injury and exsanguinating haemorrhage. Late mortality (i.e. 7 days or more after admission) is usually the result of the association of sepsis and multiple organ failure in which respiratory dysfunction plays a predominant role[1,2]. It has also been noted, in an epidemiological study of trauma deaths, that most of the patients dying from sepsis have skeletal injuries[3].

Traditionally, until the mid-1970s, the conservative management of fractures by means of skeletal traction and plaster cast immobilization had been the rule in the patient with multiple injuries. A high priority was given only to those injuries, such as certain neurosurgical, abdominal and vascular injuries, which were perceived as an immediate threat to life or limb viability. Operative stabilization of fractures on the night of admission was deemed not only unnecessary but also potentially harmful in a patient 'too sick' to withstand the prolongation of anaesthesia and the additional blood loss[4].

Cumulative evidence has since been produced to challenge this conservative approach. In 1976 Riska *et al.*[5], from Finland, claimed that, in the multiple trauma patient, the preferential use of early operative fixation of long bone and pelvic fractures has a beneficial influence on survival by preventing the 'fat embolism syndrome'. In the early 1980s, Goris' group from Holland showed that the only distinctive feature of multiple injury patients dying from sepsis was a higher Trauma Index for extremity injury[6] and, further, that in patients routinely treated with early fixation of fractures combined with prophylactic mechanical ventilation, late septic complications did not occur[7]. Meek *et al.*[8] came to a similar conclusion; 14 of their 49 patients treated by traction and cast immobilization died, while only one death occurred in 22 patients of comparable age and trauma score who were managed with rigid stabilization.

Pulmonary complications are common after long bone fractures; whether they can be ascribed to occlusion of pulmonary capillaries by macroglobules of fat is still controversial. Two recent clinical studies have demonstrated the beneficial effect of immediate fixation of long bone fractures in preventing such pulmonary complications. Lozman *et al.*[9] randomized a small number of patients to undergo either immediate fixation of all fractures or treatment by conservative orthopaedic methods; patients treated by immediate fixation had less pulmonary dysfunction. Similarly Johnson *et al.*[10] found that the delay in operative stabilization of major fractures was associated with a higher incidence of the adult respiratory distress syndrome and that this was particularly marked in the more severely injured patients. A significant contribution to the study of this issue came from Border's group in the USA. They showed that 10 days of femur traction doubled the duration of the 'pulmonary failure septic state syndrome' and almost quadrupled the incidence of fracture complications[11]. Furthermore, the postponement of orthopaedic intervention was associated with prolonged ventilatory support, a greater need for antibiotics, delayed introduction of enteral nutrition and a greater degree of sepsis[12].

Recent developments in trauma and critical care research have pointed to a link between the conservative management of skeletal injuries in multiple blunt trauma and the sequence of events that culminates in the lethal association of sepsis and organ failure. The following scenario may have been all too familiar. The patient is placed in traction in the supine position, aptly described by Border as 'the horizontal crucifixion position'[12]. The delay in mobilization predisposes to retained secretions and pulmonary atelectasis, and contributes to an increased dependence on mechanical ventilation. The post-traumatic depression of the patient's immunocompetence together with the invasive technology of the Intensive Care Unit (ICU) leads to acquired infection in the lung and other systems. The state is set for a vicious circle postponing the removal of the endotracheal tube. The recourse to ever more powerful antibiotics results in the disappearance of gut commensals and the emergence of resistant strains. The supine position, the prolonged use of sedation and ventilation, and the need for delayed orthopaedic operations all help to perpetuate the initial ileus and the inability to commence enteral feeding. Gut mucosal atrophy and alterations in

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the intestinal flora promote bacterial translocation[13] and provide an additional portal of entry for infection. In addition, the liberation of inflammatory mediators from devitalized tissues around the fracture sites may lead to widespread metabolic and nutritional consequences. These reinforce the effect of sepsis in the production of organ failure.

There seems to be an emerging international consensus regarding the advantages of early internal fixation of major fractures[14]. The approach would allow early mobilization of the critically injured and, by reducing dependence on ventilatory support and the incidence of pulmonary complications, many of the hazards inherent to a long stay in the ICU would be eliminated. There are no large-scale prospective randomized trials proving the superiority of early operative treatment of skeletal injuries. Perhaps, in the eyes of many trauma surgeons, the evidence in favour of early operation is too great to make such trials justifiable. They may be wrong. If such trials are undertaken, a close and continuous assessment of the results ought to be exercised to prevent excessive morbidity from one of the treatment options.

Total care of the multiple trauma patient is too complex to evade fragmentation. General surgeons, neurosurgeons, orthopaedic surgeons, intensive care specialists and other defined specialists are needed for their irreplaceable expertise. A surgeon dedicated to trauma management must be in charge; in our view he should ensure that patients with long bone fractures are operated upon without delay once resuscitation is completed and those injuries with an immediate threat to life have been treated.

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Br. J. Surg. 1990, Vol. 77, April, 363–364

Gallbladder cancer: the polyp–cancer sequence

Cancer of the gallbladder is the commonest malignant tumour of the biliary tract but despite many advances in diagnostic and surgical techniques, it is characterized by late diagnosis and a poor prognosis, with less than 5 per cent of patients surviving 5 years. With the increased use of grey-scale ultrasound as the investigation of choice in patients with biliary symptoms, the possibility exists for the detection of 'early' gallbladder cancers which may be cured by surgery[1]. Increased use of ultrasound will lead inevitably to the detection of other gallbladder lesions such as polyps which, until the last decade, were considered to be of little significance and unlikely to undergo malignant change[2]. Clearly if gallbladder cancer is to be detected and treated earlier, the precise relationship between benign lesions of the gallbladder and carcinoma needs to be established.

In this respect, several key questions arise: first, which benign gallbladder lesions are likely to undergo malignant change; second, what is the evidence for the malignant transformation of these lesions; third, what is their incidence; and fourth, should all gallbladder 'polyps' constitute an indication for cholecystectomy?

Much of the controversy surrounding the malignant potential of benign lesions of the gallbladder has been the result of confusion in the classification of these tumours, confusion which persisted until the report of Christensen and Ishak[3]. These workers reviewed 180 benign gallbladder lesions and established a simplified classification which is now in general use. Lesions are classed as epithelial tumours (adenoma), mesenchymal tumours (including fibroma, lipoma and haemangioma) or pseudotumours (cholesterol polyps, inflammatory polyps and adenomyoma). Adenomas may be papillary (previously called 'papillomas'), tubular or mixed and have recently been shown to have malignant potential. Recent reports suggest that adenomyomatosis may also be a premalignant lesion.

Evidence for the adenoma–adenocarcinoma sequence comes from the study by Kozuka *et al.*[4], who reviewed the histology of 1605 gallbladders and found 11 benign adenomas, seven adenomas showing malignant change and 79 invasive carcinomas, the transformation from benign adenoma into carcinoma being traceable histologically. They considered that further circumstantial evidence for the adenoma–adenocarcinoma sequence was provided by the presence of adenomatous components in all the *in situ* carcinomas and in 19 per cent of the invasive carcinomas; the correlation between the size of lesion and malignant change (all the benign adenomas were less than 12 mm in diameter, all the adenomas showing malignant change were over 12 mm in diameter and most of the invasive carcinomas were over 30 mm in diameter); and the female preponderance for both adenoma and invasive carcinoma.

Adenomyomatosis of the gallbladder is characterized by extensions of the mucosa (Rokitansky–Aschoff sinuses) into and through a thickened muscular wall. It has been described under a variety of names including diverticular disease of the gallbladder, adenomyoma, cholecystitis glandularis proliferans and cholecystitis cystica and has been thought to have no malignant potential[3]. Recent reports from Japan[5,6] and France[7,8], however, have described five patients in whom gallbladder cancer developed in areas of adenomyomatosis, suggesting that this seemingly innocent lesion may actually have malignant potential.

The incidence of gallbladder adenomas in the general population is unknown but the incidence at cholecystectomy is of the order of 1 per cent. Kozuka *et al.*[4], in their histological review of 1605 gallbladders, reported 18 adenomas (1·1 per cent). In a more recent study from Japan, Koga *et al.*[9] reported only one adenoma in 411 cholecystectomies (0·2 per cent) with adenomas forming only 3 per cent of all the benign tumours studied. The incidence of adenoma in the general population is probably little different from that at cholecystectomy and a figure of 1 per cent may be a sufficient rate for adenoma to form the basis of the majority of gallbladder cancers that occur in less than 0.002–0.016 per cent of the population per year[4].

The incidence of adenomyomatosis in the general population is similarly unknown, but it has been reported in up to 21 per cent of gallbladders removed at surgery[10] and it accounts for over 40 per cent of all benign gallbladder lesions[3].

What then should the advice be to the clinician who discovers a polypoid lesion of the gallbladder on ultrasonography? The risk of malignant change in an adenoma appears to be size dependent. The presence of biliary symptoms and/or gallstones poses

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an additional risk and thus, if either are present, cholecystectomy is recommended irrespective of the size of the 'polyp'. It should also be remembered that papillary adenomas themselves may cause biliary colic if they become detached and obstruct the cystic duct. In the absence of gallstones and symptoms, cholecystectomy is recommended for 'polyps' of 10 mm diameter or larger (as estimated ultrasonographically). If the lesion is smaller than 10 mm and the patient is asymptomatic and free of gallstones, it would appear safe to pursue a watching policy with ultrasound examinations, the frequency of which may vary for individual patients but which should be performed if possible every 6 months.

The position regarding adenomyomatosis is less clear. There is little doubt that this is diagnosed frequently on ultrasonography as it has a typical sonographic appearance[11]. In symptomatic patients with gallstones, an indication already exists for cholecystectomy so that the additional ultrasonographic finding of adenomyomatosis will not affect the management decision. If ultrasound demonstrates thickening of the gallbladder wall, however, surgery should probably be expedited because of the risk of coexisting gallbladder cancer. What should the advice be in the case of adenomyomatosis discovered by ultrasonography in asymptomatic patients or in those with biliary-type symptoms but without gallstones? Clearly it would be impractical to recommend cholecystectomy in all patients in whom this lesion is discovered 'by chance'. It may be, however, that this group of patients should undergo regular ultrasound surveillance as recommended for those with small gallbladder polyps. If ultrasonography subsequently demonstrates thickening or irregularity of the gallbladder wall, cholecystectomy should be performed.

It is only with more rigorous use of ultrasonography and a more aggressive approach towards the treatment of 'benign' polypoid lesions of the gallbladder that early gallbladder cancer can be detected and patients given an increased chance of cure.

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Br. J. Surg. 1990, Vol. 77, April, 365–367

Practicalities in the management of the acute abdomen

During 1989 *The British Journal of Surgery* published four papers[1–4] which reflect the continuing debate about the correct management of patients with acute pain in the right iliac fossa. This remains a lively issue, although it is more than 100 years since Fitz[5] coined the name acute appendicitis and established the pathological basis for early appendicectomy in 1886. When McBurney[6] described just 100 years ago the features of his first 11 patients, he made the diagnosis of acute appendicitis sound relatively simple, but he must soon have experienced some of the difficulties which continue to arise when the appendix lies behind the colon or ileum, at the brim of the pelvis, or in the abdomen of a young woman. In those days the mortality rate for acute appendicitis was 26 per cent[7], so at a time when intravenous fluid therapy was not used and antibiotics were not available, it was correct to assert that in a doubtful case it was safer to look and see rather than wait and risk perforation of the appendix. This policy was associated with a fall in the mortality rate to 4 per cent by 1912[8] and it has played a part in the reduction of the rate to its present low level of one death in every 400–500 patients[9]. However, continued use of this policy means that Hoffmann and Rasmussen[2] have still to report, in 1989, 'a usually accepted figure for negative appendicectomy of 15–30 per cent'. They are right to conclude that these high figures are 'no longer justifiable ... and can and must be reduced' because this seemingly simple operation confers little benefit on the patient and is associated with quite serious immediate and remote complications[10,11].

In seeking such an improvement it is essential to take account of the wide spectrum of conditions which can present with acute pain in the right lower quadrant, many of which do not require surgical correction. A prospective survey of children admitted to hospital with acute abdominal pain in 1965–6[12] revealed that no more than one-half required operation, mostly for appendicitis, and that 37 per cent settled spontaneously within 48 h. This survey was continued for 3 years and confirmed that about 40 per cent of children referred to hospital with suspected acute appendicitis recovered without treatment[13]. The features which helped to distinguish this syndrome from acute appendicitis were analysed, and it was named 'acute non-specific abdominal pain of childhood'. (Even with this knowledge, 14 per cent of 462 laparotomies revealed a normal appendix.) This syndrome, which soon acquired the abbreviation of NSAP, was also found to occur in over 40 per cent of adults admitted with acute abdominal pain[14]. Although many subsequent surveys in various countries have shown that this is a common condition[15] which shows for a time features suggestive of acute appendicitis, its origin remains obscure. Many follow-up studies show that only rarely do patients return with true acute appendicitis or other specific conditions[13,16].

Because NSAP remains the commonest cause of acute abdominal pain in Western countries[4,15], and can only be recognized by observing steady improvement in a patient with no other demonstrable cause for the pain, it follows that a major feature of the management of patients with acute abdominal pain must be a regime of continued observation. It also follows that, because half the patients with an acute abdomen do not require an operation, one must look very critically at any policy with a bias towards 'look and see', which leads to 15–30 per cent of appendicectomies being unprofitable.

The question is whether a policy which was correct in the circumstances of surgical practice around the year 1900 is still acceptable. In fact, there are a number of surveys which show that a critical approach to every patient admitted with abdominal pain allows a more selective policy to be adopted.

There is nothing new in recognizing that some patients with acute abdominal pain need a period of observation, but experience shows that it is worth incorporating this practice into a definite policy. Those patients who show clear signs of local or general peritonitis are immediately recognized and operative treatment arranged. Others who may be suspected of a medical cause for their pain may need side-room or radiological investigation. The doubtful cases are placed under close supervision and carefully re-examined after 2–3 hours, preferably by the same surgeon, and this is repeated as necessary. This policy of Active Observation has been carefully tested in children[16–18] and in adults[19,20] and in particular there is no evidence that any harm came to patients who were found to need laparatomy only after a period of observation. These trials, and continued experience, show that in many patients it is unwise to make a final decision on management on the basis of a single examination at the time of admission.

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Hoffmann and Rasmussen[2] rightly remark that 'appendicitis is a great leveller, an antidote to diagnostic complacency', and selective observation certainly does not eliminate diagnostic and management misjudgements, but results show that the negative appendicectomy rate generally falls well below 10 per cent. Concentration of attention on this issue, and use of a structured record form, must have made a significant contribution to these results[3], but the main finding is that a material improvement in performance can be maintained by a simple method which can be adopted without delay or expense.

Use of these methods means that management is still decided by inference from observed symptoms and signs; unless acute medical diseases such as a urinary infection or pneumonia can be diagnosed, decisions have to be directed towards advising or witholding operation. Can these decisions be based on more precise evidence provided by investigations which will point to a diagnosis? A review[2] suggests that two are of particular value.

Young women are known to have a high incidence of negative appendicectomy[21], and most of these operations are unproductive because the source of the signs is likely to be haemorrhage from a ruptured Graafian follicle or pelvic inflammatory disease. These, and other tubo-ovarian lesions, can usually be visualized at laparoscopy, which is much less invasive than laparotomy. This investigation has now had an extensive trial, and the case for preliminary laparoscopy before deciding on laparotomy in women suspected of having acute appendicitis is now established[2,3]. Its application is currently limited by the fact that general surgeons are only gradually becoming experienced in laparoscopy.

High-resolution ultrasonography can also provide an image of the acutely inflamed appendix, with a reported sensitivity of between 75 and 89 per cent[2]. Its advantage is that it is non-invasive but it is difficult to use on the obese or distended abdomen, and requires the presence of an expert ultrasonographer, which may not be easy to arrange out-of-hours.

All plans for the care of patients with an acute abdomen have to take account of the fact that a majority arrive late on in the day or at weekends, and that as much as three-quarters of emergency operating can take place after 18.00 hours[22]. Simple administrative changes can make an important contribution to good patient care. If an emergency theatre is open throughout the day about one-third of emergency operations which would otherwise have to be performed during the night can be safely deferred to the following morning[22]. This allows the urgent operation to proceed promptly, and surgeons to enjoy a little more sleep. Another important effect is that junior staff are not under pressure to operate on the doubtful abdomen before the next day's elective lists occupy theatres for many hours[23].

Although new investigations can provide welcome assistance, the assessment of the acute abdomen must continue to be predominantly a bedside exercise. No computer can provide reliable feedback without being provided with the details of an accurate history and a skilful, gentle elicitation of the physical signs. There is good evidence of the value of using a structured record form, especially if the surgeon adds a considered written opinion. Completing this exercise in itself concentrates thought, and analysis is further encouraged if regular meetings are held to compare these written opinions with the later progress of the patient. Sutton[1] and Gunn[24], with a wide experience of computer-aided diagnosis, are both clear that its main value lies in the repeated provision of another opinion, with which the bedside assessment can be compared.

As in all clinical work, there is no substitute for a consistent air of enthusiasm throughout the surgical team for a high standard of work. This is of especial importance in emergency surgery, which is often undertaken in tiring and stressful circumstances by surgeons-in-training, who do not always feel adequately supported[25,26]. It is particularly vital that senior staff are seen to regard emergency work as a field of great interest and variety, in which clinical and operative skills are tested within the span of a few hours. Their encouragement and availability for consultation and participation are of the first importance. This aspect of consultant work has important implications for surgical staffing; these have been strongly presented[23], and they need to be frequently re-emphasized until they are fully implemented.

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Review

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Asymptomatic gallstones

The increasing detection of asymptomatic gallstones leads to difficult decisions for the surgeon and patient about whether the stones should be managed expectantly or surgically. This review examines the evidence currently available upon which such decisions must be based. Gallstones may present as biliary pain, acute cholecystitis, biliary obstruction or pancreatitis, but it is not clear who will develop symptoms and what are the commonest initial symptoms. Studies of the natural history of silent gallstones suggest that a large majority of patients with such stones will remain asymptomatic. However, diabetics are at increased risk, as are patients whose stones are detected initially at laparotomy. Incidental cholecystectomy is usually safe, and preoperative detection by ultrasonic screening is an advantage in planning the operation. Prophylactic cholecystectomy is not indicated to prevent gallbladder carcinoma (except in cases of porcelain gallbladder) and there is conflicting evidence about whether cholecystectomy predisposes to colorectal carcinoma.

Keywords: Asymptomatic gallstones, silent gallstones, incidental cholecystectomy

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Despite the development of alternative methods of management[1-3] cholecystectomy remains the procedure of choice for symptomatic gallstones[4,5] provided that the patient is fit for surgery. The management of asymptomatic or silent gallstones, however, remains controversial. Some recommend no treatment[6,7], others suggest cholecystectomy in selected patients (the young, diabetics, those with a non-functioning gallbladder, those with large stones and those with a calcified gallbladder[8]) or in those undergoing laparotomy for other conditions[9], while others recommend elective cholecystectomy[10,11], particularly in patients who are under 60 years of age and in good health[12].

This review examines the evidence currently available and aims to provide more specific guidelines for the management of patients discovered to have asymptomatic gallstones. It is hoped to avoid the type of scenario depicted by Donaldson[13], where neither patient nor physician can decide upon the best course of action, the latter suggesting that the patient herself decides, and the former deciding to seek a second opinion.

Cholelithiasis: prevalence and symptoms

Cholelithiasis is common, and it is estimated that about 10–20 per cent of the adult population in developed countries have gallstones[14-19], with a higher prevalence in women[14,18-20], the obese[21,22], and in older patients[14,18,19]. That many of these stones are asymptomatic, and remain so, is not disputed. In addition, autopsy studies have shown that the majority of people with gallstones die of unrelated causes[14,20].

Increasingly, however, asymptomatic gallstones are discovered during life. Formerly detected incidentally on plain abdominal radiographs (10–15 per cent of gallstones are radio-opaque) or at laparotomy for unrelated conditions, the widespread use of diagnostic ultrasonography has led to the discovery of an increasing number of silent gallstones. It is unusual for silent stones to be detected by oral cholecystography, because unless this is employed deliberately as a screening procedure[6,21] it is unlikely to be performed in patients without symptoms attributable to biliary tract disease.

There is general agreement on what constitutes symptomatic gallstone disease, namely the occurrence of biliary pain, acute cholecystitis, biliary obstruction or pancreatitis. Upper abdominal pain not clearly due to another cause in the presence of gallstones is often ascribed to gallstones. Nevertheless even patients with apparently typical biliary pain may not be relieved of their symptoms by cholecystectomy[23], suggesting a significant degree of diagnostic inaccuracy. Painless dyspepsia is not considered to be any more frequent in those with gallstones than in the general population[6,15,18,19,24].

Why some patients with gallstones become symptomatic and others do not is unknown[25]. It may be in part a chance event, depending upon the movement of stones and their impaction in Hartmann's pouch or in the cystic duct, or their passage into the common bile duct. It follows that the relative size of the stone(s) and the calibre of various parts of the biliary tree may be important. It is clear that other factors play a role, for example acute cholecystitis may complicate other diseases[26], or occur as a postoperative complication[27,28]. The concept of stasis precipitating symptoms is important[29], and is considered to be particularly relevant in the aetiology of postoperative cholecystitis[27].

The latent period between stone formation and symptom development in those who do develop symptoms is disputed. In their small study, Mok *et al.*[30] used carbon dating techniques on retrieved stones, and concluded that there was a mean delay of 8 years between stone formation and the onset of symptoms. Gracie and Ransohoff[6] found that if stones became symptomatic, they tended to do so earlier rather than later, although they related the onset of symptoms to the time of discovery rather than to the time of formation. The findings of Lund were similar[10]. Most of the patients in his series who became symptomatic did so within 5 years.

What is the commonest first symptom of gallstones? Again the evidence is conflicting and opinion divided. Truesdell[31] found that it was not uncommon for the patient to experience a single typical attack followed by a long period of freedom from symptoms (quiescent gallstones). Ransohoff *et al.*[32] considered that uncomplicated biliary pain was by far the commonest initial manifestation of symptomatic stones (in 90 per cent of cases) and quoted a study by Newman *et al.*[33]. Pickleman and Gonzalez[34], however, found that in 77 per cent of their patients, acute cholecystitis was the first evidence of gallbladder disease. Gallstones play a significant role in the aetiology of pancreatitis, but follow-up studies on patients with silent stones[6,10,31,35,36] have generally shown a low incidence of subsequent pancreati-

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tis. Indeed pancreatitis appears to be the least common initial manifestation of gallstones.

Natural history of asymptomatic gallstones

The decision about whether to perform cholecystectomy for silent stones rests for the most part on a knowledge of the natural history of such stones and weighing the risks of expectant management against the hazards of surgery. A number of studies have addressed this problem, with conflicting conclusions.

The earlier reports by Peterson[35], Truesdell[31], and Comfort *et al.*[36] all concluded in favour of cholecystectomy, but in all these studies gallstones were initially detected at laparotomy for other conditions. The present author believes that such patients may be at particular risk of developing symptoms, and as such considers these reports later in this paper (the role of incidental cholecystectomy). More than one-third of the patients studied by Wenckert and Robertson[37] developed symptoms on follow-up, but their study group did not consist strictly of patients who were asymptomatic at the outset. Lund's group included 34 patients with asymptomatic stones[10], about one-third of whom went on to develop severe or frequent attacks of pain and one-fifth developed complications. He recommended prophylactic cholecystectomy in patients considered to be good surgical risks. It is interesting to note that this study also appeared to indicate that symptom development was less likely in men than in women.

The findings of Gracie and Ransohoff deserve special comment because their report[6] is so widely quoted, and because the data formed the basis of a subsequent paper[32] which strongly recommended expectant management of silent gallstones. From a total of 123 patients with asymptomatic stones, only 18 per cent became symptomatic during a follow-up period of 15 years. Their subjects were identified by cholecystographic screening of a healthy population. The group, faculty members of a university, comprised 110 men and 13 women, quite a different male to female ratio from the usual 'gallstone population'. The authors concluded that 'routine prophylactic operation for silent gallstone disease, at least in white American men, is neither necessary nor advisable'[6]. Although the same data were used as the basis for a later report, the qualification was dropped[32]. It should also be noted that 35 of the group underwent prophylactic cholecystectomy on the advice of a personal physician, on average 2–3 years after stone detection. More recently McSherry *et al.*[7] followed 135 patients for a mean of about 5 years, and found that 10·4 per cent developed symptoms. They recommended expectant management for silent stones.

The purpose of cholecystectomy for symptomatic gallstones is twofold, namely, the relief of symptoms and the prevention of mortality. For asymptomatic stones, these intentions must be weighed against the hazards of treatment, given the fact that most people with silent stones never develop symptoms. In an analysis comparing a policy of 'early' versus 'delayed' surgery for symptomatic stones, Hoey and Psihramis[38] found that although the 'early' strategy achieved better symptomatic relief, this was at the expense of increased mortality. Godrey *et al.*[14] even suggested that an increasing number of deaths from cholelithiasis may be related to an increasing number of cholecystectomies. Similarly, Vayda[39] suggested that the high gallstone-related mortality rate in Canada could be the result of increased surgery.

The conclusions to be drawn are that as yet there has been no definitive study documenting the true natural history of silent gallstones. However, the current evidence suggests that, since most of these patients remain asymptomatic, and given the low present day mortality rate following prompt treatment of those who go on to develop symptoms, elective cholecystectomy is not indicated in these patients. It is a further point to remember that, in a small percentage of cases, gallstones may disappear spontaneously[40].

Diabetes mellitus and asymptomatic gallstones

There has been a greater tendency for surgeons to be more aggressive in the management of asymptomatic stones in diabetics, in the belief that complications of stones occurred more commonly, and were associated with higher morbidity and mortality rates. Rabinowitch[41] and Eisele[42] showed that the results of elective surgery in diabetics with stones were at least as good as in non-diabetics. Turrill *et al.*[43] recommended prophylactic cholecystectomy for diabetics with stones, because of the fivefold increase in mortality rate that he noticed in diabetics with stone complications; Mundth[44] came to the same conclusion. More recently, however, this aggressive approach has been questioned[45].

The incidence of cholelithiasis is widely believed to be increased in diabetics, but hard evidence for this is lacking[22]. Many reports indicate that acute cholecystitis is commoner in diabetics. Sandler *et al.*[46] analysed the results obtained in 981 patients undergoing their first operation for gallstones in North Carolina and 126 were diabetic (12·8 per cent). Ransohoff *et al.*[47] studied patients with acute cholecystitis in Cleveland, and 14·8 per cent were diabetic, while 15·8 per cent of Pickleman and Gonzalez's group had diabetes[34]. These reports tend to confirm the clinical impression that acute cholecystitis is more common in diabetics with gallstones than in non-diabetics with stones.

A number of studies have shown that morbidity and mortality rates following emergency biliary surgery are higher in diabetics than in non-diabetics[43,44,46,47]. Controversy exists as to the extent to which this is so, with reported mortality rates being two to five times higher in diabetics[43,46,47]. Diabetics do require emergency surgery more often than non-diabetics[46]. By contrast, most studies do not report a significant increase in the risks for diabetics operated upon electively[41–44,48], although one report noted a higher complication rate after elective surgery in these patients[46]. However, most reports agree that any increased risk associated with diabetes is mainly attributable to a high incidence of coincidental factors (advanced age, cardiovascular disease, renal disease), rather than as a direct result of the diabetes[46,47,49–51].

What is not known is whether diabetics with asymptomatic stones are more likely to develop symptoms than non-diabetics. We can say that, if symptoms do develop, they are more likely to be severe, more likely to require emergency operation, and that such surgery is attended by a higher morbidity and mortality rate. Associated cardiovascular and renal disorders are important in increasing the risks of surgery. It appears that prophylactic cholecystectomy should be strongly considered in diabetics with incidentally detected silent stones, especially if they are free from cardiovascular and renal disease, and it follows that routine screening of adult diabetics for gallstones may also be desirable. It must be accepted, however, that our knowledge of the natural history of gallstones in diabetics is patchy.

Role of incidental cholecystectomy

Many gallstones are discovered for the first time at laparotomy for an unrelated condition, and there have been numerous reports describing the subsequent incidence of biliary symptoms if these are left untreated. Peterson[35] followed 51 such patients, 37·2 per cent of whom developed symptoms. However, not all of his patients could be classified as strictly asymptomatic at the time of original laparotomy (for pelvic disease), and the duration of follow-up is not given. Truesdell[31] followed a similar group, all women, and found that few remained without symptoms; he also recommended cholecystectomy. Comfort *et al.*[36] followed 112 cases for 10–20 years and reported that 45·5 per cent developed symptoms, but included painless dyspepsia among the symptoms attributed to gallbladder disease. The male: female ratio was not given.

There have also been a number of more recent reports addressing this topic. Schreiber's group[52] described one patient (out of four) who developed acute postoperative cholecystitis requiring surgery 8 days after his original operation, and postoperative cholecystitis is well recognized[26,27,29]. Thompson *et al.* found that 16 of their 23 previously totally asymptomatic patients developed biliary symptoms within 6 months of the primary operation[28]. Ouriel *et al.*[53] had 11 patients, eight of whom experienced biliary symptoms within a mean follow-up period of 2·9 years (one in fact dying of biliary sepsis 10 days after his original operation). Saade *et al.*[9] noted that 13 of their 25 patients became symptomatic within 2 years, while 11 of String's 17 patients became symptomatic[54]. Abdominal aortic surgery seems to be associated with a particularly high risk of precipitating symptoms in patients with previously silent stones. Numerous authors have shown that cholecystectomy may be safely performed at the time of other procedures without adding significantly to the operative morbidity and mortality rates[28,52,53,55–59]. In particular, initial fears that an increased incidence of arterial graft infection would ensue do not seem to be well founded[53,55,58,60]. One report did suggest a higher complication rate when cholecystectomy was added to abdominal aortic aneurysm repair[61], but specific factors could not be identified.

The bulk of the evidence therefore suggests that incidental cholecystectomy is not only safe but necessary. The patient's condition must be stable and the exposure adequate[52,62,63]. Routine peroperative cholangiography is not essential[28,52] and a number of authors recommend deferring cholecystectomy if common bile duct exploration is required[55,62]. With these recommendations in mind, many believe that incidental cholecystectomy should be planned, and an active search made for gallstones in those about to undergo major elective abdominal surgery[9,35]. This will allow informed consent for cholecystectomy to be obtained[63], and an appropriate incision planned, and will also diagnose the presence of stones more accurately than intraoperative palpation alone[28]. Ultrasound is the screening investigation of choice. Whether or not this policy should embrace all patients having major elective abdominal surgery remains open to question. Certainly patients undergoing major arterial surgery should be considered as at particular risk of symptom development. Similarly, those undergoing elective surgery for peptic ulcer, and major colonic surgery, could be considered suitable candidates for planned incidental cholecystectomy. A further point to note is that the majority of patients in these groups will have abdominal ultrasound performed in the course of investigations for their primary condition.

Women undergoing major abdominal gynaecological procedures form a more controversial group. On the one hand, incidental cholecystectomy would require a significant extension of the incision, and also the presence of two senior surgeons (general surgeon and gynaecologist). On the other, these patients have a definite risk of subsequent symptom development[31,35], and several reports indicate that women are more prone to develop symptoms from gallstones than men[10,18,19].

Gallstones and gallbladder carcinoma

Carcinoma of the gallbladder is an uncommon neoplasm, occurring predominantly in elderly women. The prognosis is very poor, with a 1-year survival rate of about 10 per cent, and less than 5 per cent of patients surviving 5 years[64]. There is a strong association with gallstones, which are present in at least 70 per cent of patients with gallbladder cancer, but only 1 or 2 per cent of patients with stones develop carcinoma[64]. Although a number of surgeons include the prevention of carcinoma among their reasons for advocating cholecystectomy for silent stones[11,12], and Diehl and Beral[65] calculated that one fewer death from gallbladder cancer occurs for every one hundred cholecystectomies performed during the previous year, most authors agree that it is not valid to advocate cholecystectomy for silent stones with the specific intent of preventing gallbladder cancer[10,14,64–66]. There is, however, an estimated 20–60 per cent incidence of carcinoma in the porcelain or calcified gallbladder[67–69], and cholecystectomy is recommended, symptomatic or not. Diehl[70] reported a significantly greater risk of cancer in those with larger stones, but this remains to be confirmed.

Cholecystectomy and colon carcinoma

There have been a number of reports suggesting that the risk of colorectal carcinoma is increased after cholecystectomy. The levels of secondary bile acids (notably deoxycholic acid) in bile and faeces increase following cholecystectomy, probably as a result of increased enterohepatic circulation and bacterial degradation of primary bile acids[71–73]. Experimentally, secondary bile acids have been shown to act as promoters of large bowel carcinogenesis[74,75].

Linos *et al.*[76] found a significantly increased risk of colon carcinoma in women, especially on the right side of the colon, in those who had undergone cholecystectomy, thus confirming the earlier findings of Capron *et al.*[77]. In two studies[78,79] Vernick *et al.* also found an increased risk of right-sided colon carcinoma after cholecystectomy, as did Turunen and Kivilaakso[80]. Turnbull *et al.*[81], however, found an increased risk in women but it was mainly due to a large number of rectal cancers in the study group. A study in Japan by Narisawa *et al.*[82] failed to demonstrate a significantly increased risk of colon carcinoma after cholecystectomy, and a number of other reports also failed to show an association[83,84].

On balance there is a suspicion that cholecystectomy may be associated with an increased risk of right-sided colon carcinoma in women. The complications and hazards of cholecystectomy may thus not be confined to the perioperative period, and this is an additional factor to be considered when advising cholecystectomy in asymptomatic patients.

Conclusions

Current evidence suggests that, in the majority of people with silent gallstones, expectant management is indicated, but the method of stone detection must be taken into account. In particular, those who have their stones detected incidentally at laparotomy seem to be at particular risk of developing symptoms and complications if left untreated. Screening those about to undergo major elective abdominal surgery may be useful, when preoperative knowledge of the presence of gallstones allows better planning of the incision to perform incidental cholecystectomy.

Diabetics should probably be managed differently, as they have a greater incidence of complications, and their surgical risks will increase as they develop renal and cardiovascular

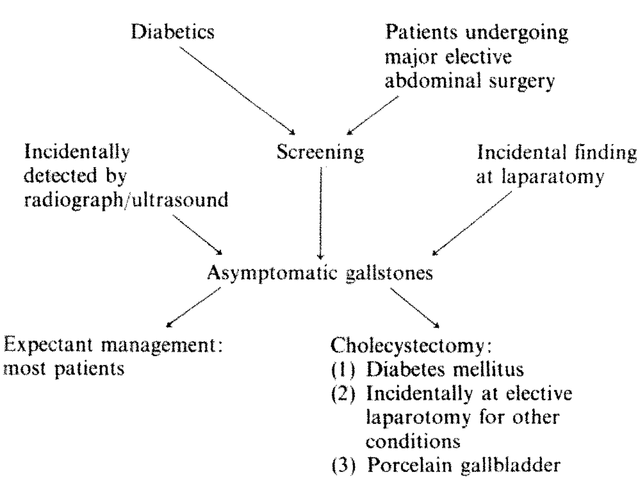
Diabetics
Patients undergoing major elective abdominal surgery
Incidentally detected by radiograph/ultrasound
Screening
Incidental finding at laparatomy
Asymptomatic gallstones
Expectant management: most patients
Cholecystectomy:
(1) Diabetes mellitus
(2) Incidentally at elective laparotomy for other conditions
(3) Porcelain gallbladder

Figure 1 *Flow diagram illustrating the suggested management of asymptomatic gallstones*

complications of diabetes. Elective cholecystectomy is advisable, and there is a strong argument for screening adult diabetics for gallstones.

Performing cholecystectomy primarily to prevent the development of gallbladder carcinoma is not justified, and the suspected association between cholecystectomy and subsequent carcinoma of the right colon serves to remind us that the complications of cholecystectomy may not be limited to the perioperative period. A flow diagram outlining the suggested management of silent stones is shown in *Figure 1*.

We still await a controlled prospective clinical trial of adequate size and duration of follow-up, based on a normal population, to define more clearly the true natural course of events for those with silent gallstones. As surgical management improves, and the risks of elective cholecystectomy decline, so too will the risks of cholecystectomy at the time of symptom development. The greatest concern here lies in the risk (as yet unknown) that these patients will only develop symptoms late in life when co-existing diseases will appreciably increase the operative mortality rate[85].

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Percutaneous arterial recanalization

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The current status of new techniques for percutaneous arterial recanalization, including laser, thermal and mechanical angioplasty techniques, is described. The reported results, potential advantages and possible future developments are discussed.

Keywords: Arteriosclerosis, transluminal angioplasty, laser surgery

Since the development of the Seldinger technique for the placement and exchange of intravascular devices over a flexible guide-wire[1], there has been increasing potential for the percutaneous treatment of occlusive vascular disease. The first experience with transluminal dilatation was by Dotter and Judkins[2] in 1964. They carried out percutaneous dilatation using a rigid catheter and this method was repeated by other workers over the next decade with some success[3]. A major advance was made with the development of a balloon for transluminal dilatation. This was first described by Grüntzig and Hopff[4] in 1974 and allowed for more extensive dilatation through a small puncture. Since that time techniques and devices have advanced rapidly and percutaneous transluminal angioplasty using a balloon catheter has gained in popularity.

Balloon angioplasty is now performed for lesions of the iliac, femoral and popliteal arteries and less commonly in other sites, such as the subclavian[5] or renal vessels[6]. Despite the expansion of angioplasty in the UK the numbers of patients subjected to surgery has not declined[7]. This suggests that balloon angioplasty is being applied to patients in whom the risks of surgery were not previously felt to be justified.

In the femoral arteries, symptoms are usually the result of complete occlusion and, although it may be possible to correct such a lesion using balloon angioplasty, the late results are relatively poor[8]. Short occlusions or stenoses in the femoral or popliteal arteries respond better[9]. Although feasible[10], the technique has not been widely used below the knee, as the vessels in this situation often have multiple total occlusions and instrumentation is difficult.

The results of percutaneous transluminal angioplasty vary considerably, probably due to the variations in patient populations, as has been noted for the results of peripheral vascular surgery[11]. For stenosis of the iliac vessels an initial technical success rate of 90–95 per cent has been reported by several workers[12,13] with a 2-year patency of 80–90 per cent. For femoropopliteal dilatation the figures are not so good and depend upon the type of lesions treated. Several workers report initial success rates of 75–85 per cent with patency of 60 per cent or less at 2 years, most of the failures being within 6 months[14]. Some subgroups of patients with long stenoses or occlusions have substantially higher failure rates[15].

The success rate clearly depends upon selecting suitable patients. A study by Mosley *et al.*[16] suggested that, if balloon angioplasty is attempted in patients with severe ischaemia, about 90 per cent of those lesions <10 cm long, and only 10 per cent of those >10 cm long, can be crossed with a guide-wire. However, the initial result following dilatation is satisfactory in only about 30 per cent of all cases. This is close to the proportion of patients thought to be suitable for balloon treatment by those that are selective in the use of percutaneous transluminal angioplasty[17], although data from the USA suggest that less than 7 per cent of patients with such lesions are actually treated by percutaneous transluminal angioplasty[18].

Since the description of successful coronary balloon angioplasty by Grüntzig[19] there has been a rapid development of techniques and devices and a huge increase in the number of procedures. This has been most marked in the USA where about 133 000 were performed[20] in 1986 and it is expected that this number will have risen to 400 000 by 1990. In the UK fewer procedures are performed, although the numbers are increasing[21].

One of the most complete reviews of the present state of coronary balloon angioplasty comes from the report of the National Heart, Lung and Blood Institute Registry[22] which has now followed two cohorts of patients in the years 1977–81 and 1985–86. In the more recent cohort, over 1800 consecutive patients were entered from a large number of representative centres. Most of the patients treated had stenoses of 15–99 per cent with only 10 per cent having complete occlusions. Overall, 8 per cent of lesions could not be crossed with a guide-wire, and for complete occlusions this figure was about one-third. There was initial clinical success in 78 per cent of patients, defined by an increase in lumen diameter of more than 20 per cent with no immediate complications. The inpatient mortality rate was 1 per cent and non-fatal infarction occurred in just over 4 per cent. Coronary artery bypass grafting was required as an emergency in 3·4 per cent and electively in 2·2 per cent. The longer-term results of this study are not yet available but other studies have suggested that the restenosis rate is approximately 25 per cent in the first 9 months[23].

New recanalization techniques

The main disadvantage of both peripheral and coronary balloon angioplasty is that it is not always possible to cannulate the vessel with a guide-wire. Even with the low failure rate reported above, the projected number of angioplasties means that in the USA alone there may be over 30 000 unsuccessful coronary recanalizations. In addition to this, there are many patients with complete occlusions in whom balloon angioplasty is felt to be impossible or hazardous and is not attempted. Furthermore, balloon angioplasty involves compression and fragmentation of the obstructing plaque against the arterial wall, and methods based upon the actual ablation of the material might achieve better short- and long-term results.

The rate of failed recanalization has halved over the past 5 years[21] and several new techniques may result in further improvements. These include a new mechanical 'drill', laser angioplasty and non-laser thermal devices. New mechanical devices for the recanalization of vessels include the Kensey device[24], the Auth mechanical rotary catheter[25] and the transluminal extraction catheter used at Duke University[26]. The latter

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two devices are intended for use over a guide-wire and are described with other debulking methods below.

Kensey device

The Kensey device consists of a cam rotating at 100 000 r.p.m., creating a vortex of accelerated fluid around it which causes fragmentation of calcified or fibrous atherosclerotic plaque into fine particles which are thought to be small enough not to cause clinical embolization in the peripheral circulation[27]. The normal arterial wall is said to be resistant to such a device. The Kensey device has now been evaluated at 16 centres including one in the UK[28]. Approximately 80 lesions have been treated in the superficial femoral artery with perforation in 16 cases and dissection of the vessel in nine. Kensey has recently reported that he is about to start a trial of the device in the coronary circulation, although the results obtained in peripheral vessels are so far no better than those obtained with alternative methods of recanalization.

Laser angioplasty

The use of a laser to ablate occlusive material in arteries was first suggested by McGuff *et al.*[29] in 1963. By the time balloon angioplasty techniques had been developed, laser and fibreoptic technology had advanced to a stage where this was a realistic possibility and in 1979 Daniel Choy filed a patent for a fibre optic delivery device for the ablation of atheromatous material[30]. Such a system may have potential advantages in allowing the recanalization of total occlusions or reducing the rate of recurrence of disease by ablation of atheromatous material.

Most of the lasers that were first used in medicine were continuous wave carbon dioxide, argon or neodymium-YAG lasers. There was no fibre optic delivery system capable of transmitting the far infrared light produced by the carbon dioxide laser, so that work concentrated on the argon and neodymium-YAG lasers. Previously, these lasers had been used primarily for applications which required heat production for coagulation or tissue welding, as in the treatment of diabetic retinopathy, retinal detachments and gastrointestinal haemorrhage. In the case of vascular recanalization, heat production and coagulation are probably undesirable and in recent years the emphasis of research has shifted to the use of pulsed lasers, similar to those used in industry for materials processing.

Bare fibre and continuous wave systems

The first system to reach the stage of clinical application was a combination of a bare optical fibre with a continuous wave argon or neodymium-YAG laser. This was the method reported for clinical work by Ginsburg *et al.*[31] and Geschwind *et al.*[32] in 1984. Ginsburg *et al.* reported 16 attempts at peripheral laser angioplasty using a bare fibre placed within a balloon catheter in the superficial femoral artery[33]. In 50 per cent of these cases the lumen was improved, but at the cost of three perforations, two dissections and two complete occlusions of previous stenoses. Other workers have also reported results with a simple bare fibre and continuous wave laser in both the peripheral circulation[34] and in the coronary vessels at the time of coronary artery grafting[35]. It has become clear that this method is unsatisfactory because of the high risk of complication, in particular of perforation when a curved or bifurcated vessel is negotiated[36]. To increase safety, modifications have been made to the fibre and a variety of detection and guidance systems has been developed.

Non-contact irradiation

The earliest papers concerned with the interaction between light and atheromatous tissue described the irradiation of tissue in air or under a transparent medium. This creates problems in occluding the vessel, producing a suitable transparent medium and adequately directing the light, particularly in curved vessels. The distance between the point of light emission and the occluding material may also be critical in producing a spot of suitable intensity to cause ablation.

Despite these limitations a non-contact system using continuous wave argon laser energy has been described by Nordstrom *et al.*[37]. The device is a specially designed balloon-ended catheter containing a 200 μm core diameter fibre with a diverging lens at the distal tip. The vessel is occluded with the balloon and perfused with heparinized saline and laser exposure is made within 3 mm of the occlusion[38]. In 48 peripheral procedures they report a primary success rate of 88 per cent (84 per cent for total occlusions) with two perforations and two distal emboli[39] (*Table 1*).

Laser thermal angioplasty devices

One of the earliest modifications to the bare optical fibre was the placement of an opaque metal probe around the tip of the fibre[40]. The delivery of continuous wave energy along the fibre led to the heating of the device which was found to be capable of recanalizing occluded arteries in animals[41]. With such a device the laser used is probably irrelevant to the clinical result so long as it does not damage the tip. This excludes some of the pulsed lasers but the device has been used successfully with both continuous wave argon[42] and neodymium-YAG lasers[43]. Experimental work showed that the tip can reach high temperatures (450–500°C) in the circulation and develop a coating of charred tissue, sometimes containing a gas bubble[44].

More recently, it has been shown that particulate debris of clinical importance may be produced by the device[45]. The original hot-tip has now been produced in several configurations and sizes ranging from 1·3 to 5 mm in diameter and a fine heated guide-wire based on the same principles is now available. The majority of clinical experience has been gained with the Trimedyne probe (Trimedyne Inc., Santa Ana, California, USA) with a size of 1·0–2·5 mm using argon or neodymium-YAG lasers at a power of 8–30 W. The device requires a few seconds to warm up to operating temperature following which attempts are made to recanalize a vessel. During use the device must be kept in constant motion because if it is kept in the same position for too long it may adhere to the vessel wall[45].

Sanborn *et al.* have now reported a 1-year follow-up of 129 femoropopliteal lesions following laser assisted balloon angioplasty[43] and Diethrich has reported 664 procedures[42] of which 54 per cent were percutaneous and 46 per cent were peroperative (*Table 1*). Recanalization rates of over 70 per cent were achieved in total occlusions in both series. Perforation rates were about 4 per cent and there were a number of restenoses which appeared at sites above or below the site of initial stenosis. Others have reported less encouraging peripheral results with distal embolization[46] or rapid recurrence of lesions[47].

Experience with the hot-tip device in the coronary circulation has been far more limited and less successful. The first four cases of percutaneous coronary laser thermal angioplasty that were reported by Cumberland *et al.*[48] resulted in two symptomatic myocardial infarctions and asymptomatic enzyme changes in a third patient. Sanborn *et al.* report 19 cases with coronary artery stenosis in which a more flexible probe was used[49]. This succeeded in passing 17 of the 19 lesions with immediate reocclusion in one and a further two closures within 5 days. Later restenosis in the first 2–12 months was observed in a further three patients. Linnemeier reports the use of the device in the treatment of 14 patients with stenosis of saphenous vein bypass grafts[50]. In one there was probe detachment and perforation resulting in tamponade. This patient required emergency surgery and later died. In another case the procedure failed and the patient subsequently died. There was one case of distal embolization and two other patients suffered from restenosis at 9 and 16 weeks following the procedure.

Rosenthal *et al.* have also reported some coronary experience using the more flexible 1·3–1·7 mm tips[51]. Four cases have been reported. In two there was failure to cross the lesion and the vessel was perforated in one of these. One was crossed and a successful balloon dilatation was performed. In a further case

Table 1 *Reported series of new percutaneous methods of arterial recanalization*

Author	System	Cases	Total occlusion (%)	Critical ischaemia (%)	Mean length of occlusion	Number of iliacs treated	Primary success (%)	Complications (no. of cases)	Reocclusions (no. of cases)
Ginsburg[33]	Argon Bare fibre	16	50	?		0	50	Occlusion of stenosis (2) Perforation (3)	Not reported
Nordstrom[39]	Argon Bare beam	48	77	?	9 cm	8	Stenosis 100 Occlusion 84	Perforation (2) Emboli (2)	5 < 24 h 6 months cumulative patency 71% (56% for occlusions)
Cumberland *et al.**[48]	Argon Hot-tip	56	100	27	8 cm	3	94	Probe detachment (1) Perforation (1)	2 < 24 h 2 more in 3–10 months
Sanborn *et al.**[49]	Argon/Nd-YAG Hot-tip	129	83	34	7 cm	0	Stenosis 95 Occlusion 73	Perforation (5) Emboli (1)	3 < 72 h, 1 year cumulative patency† – stenosis 95%, occlusion 1–3 cm 93%, 3–7 cm 76%, > 7 cm 58%
Diethrich and Bahadir[42]	Argon/Nd-YAG Hot-tip	664‡	?	?	?	?	77	Perforation 4·2% 'Spasm' 1·4% Thrombosis 4·5%	
Abela *et al.*[55]	Argon Hybrid	34	100	?	15 cm	1	91	13 proceeded to surgery	2 of 15 with 6 month follow-up
Litvak *et al.*[61]	Excimer (308 nm) Single/multifibre	23	70	?	43% over 10 cm	0	Occlusion 81 Stenosis 71	None	4 (mean follow-up 4 months)
Michaels *et al.*[64]	Pulsed Nd-YAG Sapphire	37	100	59	16 cm	0	73	Perforation (1) Skin reaction (1)	7 < 24 h 1 other (median follow-up 7 months)
Lammer and Karnel[65]	Argon/Ng-YAG Hot tip/sapphire	88 (14/74)	100	50	8 cm	0	Hot-tip 79 Sapphire 82	Aneurysm at 6 months (1) Perforation (8) Emboli (1)	2 < 24 h 9 of 58 followed to 6 months
Murray and Wood[68]	Pulsed dye Ball-tip	10	100	?	21 cm	0	90	None	2 < 48 h
Leon *et al.*[71]	Pulsed dye Probe and fire	14	100	?	7 cm	0	80	Perforation (3) (? due to guide-wire)	2 < 24 h
Rees and Gehani[28]	Kensey device	10	100	?	2–16 cm	2	70	None	100% patency at 3 months
Simpson *et al.*[73]	Atherectomy device	172	0	27	0	8%	note§	Thrombosis (2) Emboli (1)	
Stack *et al.*[26]	Transluminal extraction catheter	33	0	?	0	0	95¶	None	

* These series may have cases in common. † Based on initial successful recanalization. ‡ Includes several cases undergoing multiple procedures. § Mean improvement from 86 per cent to 22 per cent stenosis. ¶ Success defined as < 50 per cent residual stenosis

the obstruction was crossed without applying energy but, when attempts were made to debulk the lesion using the laser, the patient developed intractable arterial spasm.

Both experimental and clinical work with the hot-tip method in the peripheral and coronary circulation are starting to show some problems that may well be related to thermal damage and debris formation[52].

Hybrid laser thermal probe

It has been shown that the hot-tip device is incapable of crossing some fibrous and calcified lesions[53]. In an attempt to overcome this, a hot-tip device has been developed which has a sapphire window to allow some of the light to fall directly upon the tissue[54]. Some experience has been gained with this device in the peripheral circulation[55,56]. The configuration is a 2 mm open-ended metal cap with a small sapphire lens recessed in the tip. An argon or neodymium-YAG laser is used to drive this with output of between 1 and 10 W and the results of 34 cases have been reported (*Table 1*).

Non-laser thermal angioplasty

The apparently successful hot-tip device in which a metal probe is heated by a laser has been followed by the development of a heated probe that does not use a laser power source. One such device consists of a portable electrical source that delivers up to 40 W of radio frequency energy to heat a gold bullet-shaped tip of 2 mm diameter to 550°C in air[57]. Other similar devices have also undergone trials[58], and experimental work *in vitro* and *in vivo* has shown that it is possible to recanalize vessels, with histological effects similar to those produced by hot-tip laser angioplasty. Only preliminary results have so far been published[59], but it seems unlikely that the results will be better than those of the laser-heated hot-tip device described above, and although the equipment may be less expensive, the cost of disposables is likely to be high.

Multiple fibre devices

There are several potential advantages in using a bundle of small fibres in an angioplasty device. A comparatively large atraumatic tip may be produced without the need to expand the laser beam. High power transmission may be obtained and a bundle can be made more flexible than a single large fibre of comparable diameter.

Several devices have been designed on this basis. A system for use with an argon laser has been described by Cote. This consists of a ring of fibres around a central guide-wire channel, the fibres being used to deliver continuous wave energy from an argon laser. The device has been used in a small number of patients in the coronary circulation[60]. A guide-wire is first passed through a stenosis and then the laser is used to enlarge the channel through the stenotic region. In all cases this procedure has been followed by balloon angioplasty. Since the procedure has been combined with mechanical recanalization using a guide-wire and subsequent balloon angioplasty, it is difficult to assess the part played by the laser and no long-term follow-up is yet available.

A similar system has been described for use with an excimer laser. A 308 nm Xe-Cl laser has been coupled to two separate fibreoptic devices. One is a single bare fibre within an attached catheter that is used to recanalize complete occlusions, and the other is a 5 Fr laser catheter, consisting of a ring of fibres for passage over a guide-wire, that is used to debulk stenotic lesions. Twenty-three patients with peripheral lesions have been treated with 13 of 16 total occlusions being successfully recanalized and five of seven stenoses being successfully reopened[61] (*Table 1*). A single case in which a similar system was used in the coronary circulation has recently been reported[62].

Sapphire tipped devices

Artificial sapphires are very transparent to laser light from ultraviolet to infrared wavelengths and are made in a variety of shapes. For some years they have been available for laser surgery and have usually been used for cutting and ablation of tissue by contact with a laser probe[63]. A 2·2 mm hemispherical sapphire has been used with a pulsed neodymium-YAG laser for the treatment of 37 completely occluded superficial femoral arteries[64] and Lammer and Karnel[65] have described the use of a similar device with a continuous wave neodymium-YAG laser. In this series, 14 procedures with the hot-tip system were compared with 74 using the sapphire device. It was concluded that the sapphire has some advantages, but the series is small and not randomized and the differences are not significant.

Sapphire has also been used in other devices such as the hybrid probe described above and also as a transparent window at the tip of a multiple fibre device[66].

Ball-tip devices

Although experimental work has been reported using a lens or ball-tip device[67], there has been very little clinical application of this technology because of previous problems that have been encountered in producing reliable and mechanically sound devices. A small number of open peripheral angioplasties of the superficial femoral artery have been carried out using a ball-tip device in combination with a pulsed dye laser[68].

Directing and sensing devices

In order to improve the safety of laser angioplasty some form of sensing device or guiding device might be used to reduce the risk of vessel perforation. Such techniques might be an adjunct or an alternative to the modification of a fibre tip. There are several potential methods for carrying out such guidance. Small angioscopes with good resolution are now being produced and have been used at the time of laser angioplasty[69].

Two devices have been described which make use of the detection of tissue fluorescence to ascertain the nature of the tissue against which the fibre is placed. The first of these is a multiple fibre device in which fluorescence is elicited from a number of small fibres and the fluorescence pattern is analysed by computer[70]. This determines which of the fibres is against the most diseased area of tissue and controls the firing of a laser down the appropriate fibre. Although some experimental work has been reported with this device it has not as yet been reported in clinical use.

The fluorescence-guided laser angioplasty device (MCM Laboratories, Mountain View, California, USA) is also based upon this principle. It uses a single fibre through which a pulse of exciting light from a helium–cadmium laser is delivered. The fluorescence pattern is then analysed by computer to decide whether the device is against normal or abnormal tissue. So long as the device is against abnormal tissue the fibre is used to deliver a pulse of light from a dye laser. Such a device has been shown to be capable of discriminating quite accurately between normal endothelium or media and atheromatous tissue[71] and initial clinical results have been reported[72] (*Table 1*).

Other techniques

It has been suggested that removal of plaque by laser ablation or some other mechanical method could reduce the rate of disease recurrence following balloon angioplasty. Several mechanical devices have been designed and used clinically in both the peripheral and coronary circulation. Two other devices which are intended to improve the long-term patency of balloon dilated segments are the Spears' laser balloon and the intravascular stent. These are not themselves methods of recanalization but they may both serve to maintain patency after recanalization.

Simpson device

This ingenious mechanical device consists of a catheter which passes over a guide-wire, the end of the catheter forming a chamber with a side slot on one side and a small balloon on the other. The slot contains a circular blade which rotates at 2000 r.p.m.[73]. The catheter is placed in the stenosis over a guide-wire and the balloon is inflated to 20–30 p.s.i. to hold the slot against the atheromatous plaque which is then cut by advancing the rotating blade. The device can then be rotated and several cuts made to debulk the atheromatous plaque. After a number of passes it is removed and the excised material is cleared from the chamber.

Simpson *et al.* report on the use of this device on over 200 lesions in the peripheral arteries, most of which were in the superficial femoral artery[74]. They had a primary success rate of over 90 per cent with no perforations or dissections and one acute occlusion. They have now also carried out over 50 procedures in the coronary circulation[75], most of which were for restenosis following balloon angioplasty. Seventy-five per cent were initially clinically successful, with the remainder requiring balloon angioplasty. There were four complications, one of which was treated successfully with balloon percutaneous transluminal angioplasty, one with streptokinase, and one with urgent bypass surgery. The other resolved without treatment.

The initial results appear to be good in both the peripheral and coronary circulations but it remains to be seen whether they can be repeated by other workers and whether the new procedure is justified by a lower rate of restenosis.

Mechanical rotary catheter

Another high speed rotating device has been described which consists of a flexible rotating shaft with an abrasive tip of 1·25–1·75 mm diameter. This is passed over a guide-wire under fluoroscopic control and the tip is advanced and retracted several times through the stenosis[76]. Eleven patients have undergone treatment at the time of insertion of a coronary artery bypass graft. Ten out of 11 segments of stenosed vessel were recanalized using the device, with one perforation[77]. Five percutaneous cases have been carried out with no immediate complications[78]. Again, it is likely to be some time before the potential of this device can be assessed by follow-up studies.

Transluminal extraction catheter

This device, which has been developed at Duke University, consists of a rotating stainless steel conical cutting head which rotates at 750 r.p.m. and is inserted over a guide-wire. The cutting head is mounted on a tube with a vacuum system which retrieves the excised material[26]. In 33 peripheral lesions treated so far there has been no perforation or distal embolus and the radiological result has been successful in 95 per cent of cases. One patient with a coronary stenosis has also been treated[26] but the immediate or long-term results are as yet unknown.

Spears' balloon

The Spears' balloon consists of an angioplasty balloon with a central diffusing tip of an optical fibre through which laser energy can be delivered. The use of a laser to produce heating over the surface of the inflated balloon has been shown experimentally to result in temperatures between 95°C and

140°C at the parameters which were used[79]. A strong weld can be produced between intima and media by the combination of pressure and heat[80]. The technique was originally suggested for the welding of intimal flaps, but it has now been suggested that this may be extended for all balloon angioplasties, in order to reduce the rate of late restenosis[81]. There is, however, little evidence that intimal dissection is a frequent cause of late restenosis, or that heating the arterial wall is likely to reduce its occurrence. The device has now been used in clinical percutaneous coronary angioplasties with some slight increase in the extent of dilatation[82] but there is as yet no long-term follow-up.

Intravascular stents

The use of an intravascular stent to maintain patency after percutaneous transluminal dilatation was first suggested by Dotter[83] in 1969 and a variety of stents has since been developed. Sigwart *et al.* have described a stainless steel, self expanding stent which can be introduced through a small diameter delivery catheter[84] and this has now been used for the emergency treatment of acute occlusion after percutaneous transluminal coronary angioplasty[85], for vein graft stenosis[86], and for recurrent stenosis after percutaneous transluminal coronary angioplasty[84]. They have reported a total of 60 cases, with four acute occlusions and one sudden death[87]. All complications occurred in 26 patients treated for restenosis of the left coronary artery. Another form of stent has been described which is mounted on the outside of a balloon catheter and is dilated by the balloon, thereby remaining in the artery following dilatation[88]. This device has been used in six patients for acute closure following percutaneous transluminal coronary angioplasty, with initial success in five. Nevertheless, all patients then proceeded to coronary artery bypass grafting[89]. Four similar stents have been placed in the right coronary artery for restenosis. One of these was misplaced although all vessels remained patent at 1–5 months. Thirty-one patients have undergone implantation of stents in the iliac arteries with some initial improvement in 28 but acute thrombosis in one[90].

Although it appears possible to place various types of metal stent in both the coronary and peripheral circulation, there is little evidence that this results in improved patency[91]. Acute thrombosis can occur following the placement of a stent and it will take considerable work to show whether or not this risk is outweighed by better long-term patency.

Conclusion

Several new techniques for transluminal treatment of occluded vessels are undergoing clinical evaluation. As yet, none has had sufficient use for its clinical potential to be accurately assessed, and comparisons between devices are made difficult by differences in definitions, patient selection and methods of reporting results. Many of the available systems are intended to serve different purposes. Some are for the initial recanalization of vessels which would not, otherwise, be amenable to percutaneous treatment, whilst others are used over a guide-wire and are intended to improve the long-term patency after treatment for lesions that would be amenable to conventional balloon percutaneous transluminal angioplasty.

For recanalization of total occlusions, appreciable clinical experience has only been reported with the hot-tip and sapphire laser devices and the mechanical Kensey device. Initial reports suggest that some centres using these devices are attempting percutaneous treatment of occlusions which would previously have been treated surgically and that they are obtaining promising results. It will require prospective, randomized, controlled trials to show that such methods have advantages over the use of conventional guide-wire techniques. Some such trials have already begun[92] but it is likely to be several years before the results emerge.

The 'over the wire' methods will be even more difficult to assess. When such methods are applicable, balloon angioplasty should be possible and in view of the present results of the latter, it will require a large controlled trial with considerable follow-up before any advantage of the 'over the wire' treatments becomes obvious. In several of the methods, the theoretical and experimental backgrounds are rather dubious. However some, particularly the Simpson atherectomy device, appear to show promise for selected groups of patients.

It would be easier to compare methods if there were an accepted way for results to be calculated and presented. In relevant published series the incidence of critical ischaemia varies from zero to almost 60 per cent, the proportion of stenotic lesions from zero to 100 per cent and mean occlusion length can be anything up to 21 cm. Indeed, such figures are not always reported. More seriously, there is inconsistency in the basis for reporting results, with 'cases' referring variously to patients, limbs, procedures or lesions. Long-term patency rates may be judged by clinical assessment, by pressure indices or by imaging, and calculations may be based upon all cases or only upon the initial successes.

There is a large potential market for any device which can be shown effectively to recanalize completely occluded peripheral or coronary arteries. This has led to massive investment in the development of such techniques. The high costs of research and development have led companies to push systems rapidly into clinical use. None of the current laser systems has proven clinical advantages or is sufficiently safe for routine use in the coronary circulation. It seems likely that some means of guidance or sensing will be necessary before coronary laser angioplasty becomes a realistic possibility.

Percutaneous vascular recanalization is a new field of surgery which has undergone rapid growth over the past few years. At present there is no new system that has been shown to offer advantages over established techniques, but, if current progress is maintained, it seems likely that most arterial occlusions will eventually be amenable to transluminal treatment without the need for major vascular surgery.

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Graduated compression stockings in the prevention of postoperative deep vein thrombosis

This review examines the role of graduated elastic compression stockings in the prevention of postoperative deep vein thrombosis. Used alone compression stockings reduce the incidence of postoperative deep vein thrombosis by approximately 60 per cent and when used in combination with other preventive methods, such as low dose heparin or intermittent calf compression, they further reduce the incidence by up to 85 per cent.

Keywords: Thrombosis, deep vein thrombosis, graduated compression stockings

Forty years ago venous thromboembolic complications were well recognized as a major factor contributing to perioperative morbidity and mortality. The aetiological factors implicated in thromboembolism in these patients were thought largely to be the result of venous stasis. In a paper in 1941 reporting on 351 autopsies, Hunter and his colleagues stated that, in their opinion, the major cause of lower limb deep vein thrombosis was the sudden confinement to bed of previously ambulant elderly patients who were thus deprived of exercise and gravity to maintain their venous circulation[1]. As long ago as 1949, increased venous flow had been demonstrated in limbs subjected to local compression, by observing the time taken for substances injected into the foot to appear in, and be cleared from, the common femoral vein[2]. Subsequent clinical studies using radioactive isotopes confirmed the reduction in transit time between the foot and femoral vein produced by compression[3,4]. On theoretical grounds elastic compression became one of the first suggested methods for prevention.

Although it has been demonstrated that elastic compression decreases the venous capacitance of a limb, the resultant alteration in blood flow velocity through the femoral vein is dependent upon the pressure gradient applied to the limb. Compression applied in a decreasing gradient from distal to proximal will produce maximal increase in femoral venous flow velocity[5]. Compression of the leg with elastic bandages, no matter how carefully applied, may cause an inverse gradient as a result of the garter effect, resulting in delayed venous emptying[6]. Full length stockings, if not properly designed, may cause constriction by rolling down the thigh and forming a 'garter'. The application of poorly designed compression stockings, particularly in the form of tubular stockings, undoubtedly resulted in the early failure to demonstrate the efficacy of this form of prophylaxis[7–9].

Graduated compression stockings of relatively low pressure (18 mmHg at the ankle decreasing to 6·5 mmHg at the upper thigh) have been shown, using Doppler flow velocity measurements, to increase blood velocity in the femoral vein. This increased velocity persists for 30 min after the stockings are removed in patients at bedrest, due possibly to persistence of venous tone engendered by the compression stockings[5]. In addition to the observation of increased blood velocity in legs fitted with graduated compression stockings, faster clearance of contrast material from the veins and from behind the venous valve cusps has been demonstrated[6]. Controlled comparative studies of the effects of compression stockings on venous flow in recumbent patients have used full length stockings in all but two instances[10,11]. The effect of below knee compression has been compared with full leg compression, and it has been shown that a compression pressure of 18 mmHg at the ankle reducing to 14 mmHg at the upper calf is as effective in increasing deep venous velocity as a full length pressure gradient from 18 mmHg at the ankle to 8 mmHg at the upper thigh[12]. A recent study comparing above and below knee stockings failed to demonstrate a statistical difference in the incidence of postoperative deep vein thrombosis. In the below knee group one of 58 patients (1·7 per cent) and in the above knee group four of 56 patients (7·1 per cent) suffered a postoperative deep vein thrombosis[10].

In recent years it has been suggested that compression stockings also prevent passive dilatation of the veins to the point where the media no longer provides support for the endothelial layer so that endothelial tears occur[13]. In the presence of such tears and influenced by activated clotting factors and venous stasis (which occurs during operation) white cells migrate under the venous endothelium. The latter is eventually shed exposing the underlying thrombogenic subendothelial collagen. In the study of Comerota *et al.*[14] the progressive dilatation of forearm veins throughout the course of operation was followed using B-mode real time ultrasound scanning. An increased incidence of deep vein thrombosis, detected in the legs using the ^{125}I-labelled fibrinogen test, was found in patients in whom the venous diameter had increased by more than 20 per cent. It has thus been suggested that compression stockings might inhibit two elements of the aetiological triad of venous thrombosis, namely stasis and damage to the vessel wall.

The efficacy of graduated compression stockings in the prevention of deep vein thrombosis

In 1952 the first major controlled study of elastic stockings in the prophylaxis of thromboembolic complications reported one post-mortem but non-fatal pulmonary embolus in 100 deaths from 2346 treated patients compared with six pulmonary emboli (two fatal, four non-fatal) in 89 deaths in 2395 untreated controls. The post-mortem rate was 64 per cent and 51 per cent respectively[15].

Following the introduction of the ^{125}I-labelled fibrinogen test[16] an unexpectedly high incidence of postoperative lower limb thrombosis was demonstrated and numerous studies were mounted to determine the efficacy of various prophylactic methods. A large number of studies have examined the role of low dose heparin which, in a recent meta-analysis of published trials, has been shown to reduce the overall incidence of postoperative deep vein thrombosis from 27 per cent in controls to 9·6 per cent in treated patients[17], thus setting the standard against which other preventive methods have been compared.

Early studies in the UK failed to demonstrate the efficacy of lower limb compression[7–9,18]. One of these studies, using historical controls, used below knee elastic stockings[18], while

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Table 1 *The incidence of deep vein thrombosis detected with the ^{125}I-labelled fibrinogen test in studies using graduated compression stockings*

Trial	Number of patients	Control deep vein thrombosis	Stocking deep vein thrombosis
General surgery			
Tsapogas *et al.*[19]	95	6/44 (14)	2/51 (4)
Holford[20]	95	23/44 (49)	11/48 (23)
Scurr *et al.*[21]	70	26/70 (legs) (37)	8/70 (11)
Borow and Goldson[22]	201	34/95 (36)	15/106 (14)
Allen *et al.*[23]	197	37/100 (37)	15/97 (15)
Inada *et al.*[24]	110	16/110 (legs) (14)	4/110 (4)
Fasting *et al.*[25]	100	6/46 (13) (LDH)	6/54 (11)
		143/463 (31)	61/536 (11)
Hip surgery			
Barnes *et al.*[26]	18	5/10 (50)	0/8 (0)
Ishak and Morley[27]	76	22/41 (54)	7/35 (20)
Gynaecological surgery			
Turner *et al.*[28]	300	16/150 (11)	2/150 (1·4)
Turner *et al.*[28]	196	4/92 (4)	0/104 (0)

Values in parentheses are percentages. LDH, low dose heparin

Table 2 *The incidence of deep vein thrombosis detected with the ^{125}I-labelled fibrinogen test in studies using graduated compression stockings combined with an additional treatment*

			Incidence of deep vein thrombosis	
Trial	Number of patients	Additional prophylaxis	Additional agent only	Additional agent and stocking
General surgery				
Törngren[29]	98	Low dose heparin	12/98 (12)	4/98 (4)
Wille-Jorgensen *et al.*[30]	176	Low dose heparin	11/90 (12)	2/86 (2)
Borow and Goldson[22]	56	Low dose heparin	15/56 (27) (control, no prophylaxis)	2/63 (3)
Scurr *et al.*[31]	78	Intermittent calf compression	7/78 (legs) (9)	1/78 (1)
Bergqvist and Linblad[32]	80	Dextran	8/80 (legs) (10)	0/80 (0)

Values in parentheses are percentages

the others used cylindrical tubular stockings compression sleeves not always adjusted for the size of limb and likewise fitted only to below the knee. It is now recognized that this type of compression exerts a garter effect in the upper calf and thigh reducing the efficacy and aggravating stasis. Subsequently, several studies have been published, demonstrating reduction in the incidence of postoperative deep vein thrombosis in patients fitted with graduated compression stockings when compared with controls. Overall, elastic compression stockings reduce the incidence of postoperative deep vein thrombosis by approximately 60 per cent, i.e. from 31 per cent to 11 per cent in general surgical patients, and a reduction has also been demonstrated in patients undergoing orthopaedic and gynaecological procedures, although the numbers studied in these groups are smaller. The results of these studies are summarized in *Table 1*. The majority of these studies used T.E.D. (thromboembolism deterrent; Kendall Co., Boston, Massachusetts, USA) stockings. In two the make was not mentioned. In a further three studies C.A.R.E. (American Hospital Supply, McGaw Park, Illinois, USA), Beiersdorf AB (Kungsbacka, Sweden) and Brevet (Brevet Hospital Products, Reading, UK) stockings were used respectively. However all makes of stocking provided decreasing graduated compression from ankle to calf and thigh.

Because of the realization that multiple factors are involved in the pathogenesis of deep vein thrombosis, and the failure of any single method of prevention to abolish deep vein thrombosis, prophylaxis using more than one antithrombotic agent has been tried. As early as 1974 Rosengarten, using three modalities, low dose heparin, peroperative electrical calf stimulation and elastic stockings, was able to abolish postoperative deep vein thrombosis in patients undergoing hip surgery[19]. Compression stockings have been used in conjunction with low dose heparin (three studies)[22,29,30], intermittent calf compression (one study)[31] and dextran 70 (one study)[32], reducing the incidence of deep vein thrombosis even further (*Table 2*).

Other studies have used intermittent calf compression both during operation and in the early postoperative period followed by graduated compression stockings until discharge, with an overall rate of postoperative deep vein thrombosis of 4 per cent[31]. In the only study where graduated compression stockings were worn continuously in conjunction with intermittent calf compression applied both intra- and postoperatively, a further reduction in the incidence to 1 per cent was achieved[32].

Intermittent pneumatic compression and graduated compression stockings used in combination have the advantage of relatively low cost per patient and no associated bleeding complications. They have the disadvantage of logistics, with a large number of machines being required for routine postoperative use and some patient resistance militating against widespread use in smaller centres. It has been argued that, if it could be shown that the combination of graduated compression stockings used throughout the patient's stay in hospital and intermittent calf compression used intraoperatively only was as effective, the number of machines required by each hospital would be significantly reduced leading to more widespread and more cost effective usage. One group[33] has addressed this aspect studying 114 patients randomized to receive either low dose heparin and dihydroergotamine or intraoperative intermittent calf compression and graduated compression stockings which were applied randomly to one or other leg of patients having major abdominal surgery. The incidence of deep vein thrombosis was two of 54 (4 per cent) in the heparin group and ten of 54 (19 per cent) in the compression group. The addition of graduated compression stockings to one leg did not influence the distribution of postoperative deep vein thrombosis. The use of the opposite leg as a control could be criticized, and further studies are required to compare patients wearing compression stockings given either intraoperative intermittent compression or intermittent compression continuing into the postoperative period to clarify this aspect. The continuation of intermittent calf compression into the postoperative period may, however, be important.

Currently, although most surgeons believe that prophylaxis should be adjusted according to the level of risk, both for postoperative deep vein thrombosis and potential bleeding complications in individual patients, there are many contradictions in the claims for the various prophylactic regimens and the conflicting recommendations are confusing. Not every prophylactic regimen is suitable for every patient with the result that the various methods must be tailored to fit individual requirements based on the predicted risks of thromboembolism on the one hand and potential bleeding complications on the other. Patients can be divided on clinical grounds into several risk groups, for example: low risk (<6 per cent), moderate risk (6–40 per cent) and high risk (>40 per cent) of developing postoperative deep vein thrombosis[34]. The high risk group would include patients undergoing major intra-abdominal, pelvic and hip surgery, as well as those with hip fractures, major pelvic and thigh trauma, malignant disease, a past history of thromboembolism and those taking oral contraceptive agents.

Graduated compression stockings should be used for all levels of risk, they are relatively inexpensive, easy to use, safe and acceptable to patients. Care, however, must be taken in any patient with peripheral vascular disease that the ischaemia is not aggravated by the compression and this condition is a relative contraindication to the use of compression stockings. Low risk patients need no further prophylaxis. There are three options in the further management of the moderate and high risk groups: (1) no further prophylaxis and thus management on an intention to treat basis when a diagnosis of thromboembolism is made; (2) thromboembolism surveillance which is very effective but extremely expensive and time consuming – this is probably only indicated in extremely high risk patients where adequate prophylaxis cannot be given for any reason; and (3) an additional prophylactic method. We would recommend the third option, using either low dose heparin, low molecular weight heparin, or intermittent calf compression as an additional agent, and the one selected would depend on the type of operation being performed (heparin being absolutely contraindicated in intracranial and spinal surgery), the risk of bleeding complications (haemorrhagic diathesis or extensive dissection) and local hospital routine, all beyond the scope of this review. Ideally, in patients at high risk two additional prophylactic agents need to be added to the compression stockings for maximum preventive effect.

In summary, graduated compression stockings are important in the prevention of postoperative deep vein thrombosis. Their effectiveness has only been fully realized in the last decade.

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Announcements

ASSOCIATION OF SURGEONS IN TRAINING

Membership of the Association is open to all senior registrars holding accredited posts in general surgery, urology, plastic surgery, neurosurgery, orthopaedics, cardiothoracic surgery and paediatric surgery. Registrars in the above specialties who are 2 years post-fellowship may also apply. The Association represents the views of members on all matters relevant to surgical training besides holding scientific and social meetings. If you are not a member please contact the Secretary, Barney Harrison, 6 Kyveilog Street, Pontcanna, Cardiff CF1 9JA, for details of membership, local representatives and forthcoming meetings. The next AGM will be held in Birmingham from 20–22 September 1990.

RACS VISITING REGISTRAR TRAVELLING FELLOWSHIP

Applications are invited for the above award from surgeons in training holding a UK Fellowship who are current or prospective members of the Association of Surgeons in Training. Applicants should have an established research background and currently hold either Career Registrar, Research Fellow or 1st year Senior Registrar posts. The successful candidate will visit New South Wales teaching hospitals, from 6–19 August, and will formally present original work at the Annual Scientific Meeting of Surgical Fellows of New South Wales. The award will cover a return air fare (UK – Sydney), all accommodation and transport whilst in New South Wales and an honorarium. Applicants should send a brief curriculum vitae, an abstract of the proposed research presentation and an accompanying letter to B. J. Harrison, Honorary Secretary ASIT, 6 Kyveilog Street, Pontcanna, Cardiff CF1 9JA. Closing date for applications is 15 April 1990. Shortlisted candidates will be required to attend for interview at the Royal College of Surgeons.

For debate

Statistical comparison of two methods of clinical measurement

An article published last year in The British Journal of Surgery (*Br J Surg* 1989; **76**: 72–5) *provoked a considerable response. We present below a copy of the title and abstract of the original paper, two letters which refer to it, and a paper written by Dr G. D. Murray, statistical consultant of the* journal, *and Mr R. Miller. This paper examines the criticisms in the letters.*

Air-filled microballoon manometry for use in anorectal physiology

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Manometry is fundamental to anorectal physiology but the water-filled manometric systems commonly used have several disadvantages. To investigate the 'new' air-filled microballoon system, we compared it with a standard water-filled equivalent by measuring sphincter length, maximum resting pressure (MRP) and maximum voluntary contraction pressure (MVC) in 44 patients using the station pull-through technique. A good correlation was found for all three parameters (Spearman correlation coefficient r_s: sphincter length = 0·86, MRP = 0·86 and MVC = 0·94, $P<0{\cdot}001$). Repeat studies in 15 patients showed excellent reproducibility (r_s: sphincter length = 0·97, MRP = 0·96 and MVC = 0·96, $P<0{\cdot}001$). Air-filled microballoon manometry gives results similar to a water-filled microballoon system and has many advantages.

Letter 1

Sir

We wish to comment on the paper by Miller *et al.* which recently appeared in *The British Journal of Surgery*. The authors make a number of errors in their use of statistics and in the presentation of their data with consequent inappropriate conclusions.

Although the authors say they have used the statistical method described by Bland and Altman[1], by using correlation statistics in the analysis of their data and making errors of construction of their graphical presentations the authors have given a clear demonstration of how easy it is to become misled.

Bland and Altman showed that the use of correlation for comparing two methods of measurement is misleading and inappropriate and gave a simple method of calculating the bias between two methods of measurement, in addition to an improved method of graphical presentation than the x–y plot used for correlation.

A correlation coefficient measures the strength of a relation between two variables, not the agreement between them. It is hardly surprising that the pressures recorded by the air-filled system were related (correlated) to the pressures recorded by the water-filled system from the same group of patients, just as lengths recorded by a centimetre rule would be related to those recorded by an inch rule in the measurement of the same pieces of string. What matters is not whether there is correlation but whether there is agreement between the actual numerical values obtained by the two methods of measurement.

They have attempted to use the graphical method described by Bland and Altman. This would have allowed them to see large differences and lack of agreement between the two techniques. However, two errors have led them to construct misleading figures (*Figures 5a, b* and *c*). First, in these figures the line indicating the calculated mean difference is incorrectly shown as passing through zero (indicating no mean difference, or bias). In *Figure 5a* the majority of the data points lie above this line and the mean difference should be larger than zero indicating a positive bias. In *Figures 5b* and *c* the majority of the data points lie below this line, indicating from their graphs that the mean difference should be about $-20\ \mathrm{cmH_2O}$ and $-40\ \mathrm{cmH_2O}$ respectively.

Second, in addition to the large negative bias for the agreement between the methods for the maximum resting pressure and maximum voluntary contraction pressure the graphs also show clearly that the difference in agreement increases as the estimated pressure increases. This means that the bias between the systems is not uniform across the measured range and is a further demonstration of the unreliability of one or both methods of pressure measurement. Bland and Altman indicated that logarithmic transformation may be appropriate in this situation.

Had these calculations been made and plotted correctly an important additional calculation would be the 95 per cent confidence intervals of the calculated bias. In our opinion looking at the data distribution in *Figures 5b* and *c* these are likely not to encompass zero. In other words the two methods of measurement would give statistically different results, contrary to the conclusions made by these authors.

There was no proper recognition by the authors of the large systematic bias between the two methods, just a weak remark in the final discussion that 'the air system gave results that were in general lower'. In the abstract, however, where they do comment on comparability (last sentence) they observe that the two methods give similar results. We feel this is a major distortion of what they found.

We feel that the authors should be required to publish an addendum in the *journal* quoting the correct bias, 95 per cent confidence intervals and limits of agreement by the two methods of measurement along with correctly drawn figures and the appropriate conclusion that these two methods of measurement do not agree. Further light could be shed on the disagreement between the two methods by presenting the reproducibility data in a similar way, rather than as correlation coefficients.

We would also encourage them, in this addendum, to publish the data of the comparison of the two systems (water- and air-filled) against the reference pressure source used in their calibration procedure (i.e. the mercury sphygmomanometer). Clearly, from the points made above, at least one, if not both, of the systems performs poorly.

The recent review by Murray[2] commented on the quality of statistical methods, presentation and interpretation of data in papers in the *journal*. We hope that this indicates that the *journal* intends to increase the level of statistical scrutiny of submitted papers.

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Letter 2

Sir

I enjoyed the paper by Miller *et al.* detailing their comparison of air-filled and water-filled balloon systems for anorectal manometry, despite being rather confused by their statistical analysis.

There has been an attempt to use correlation as a method of assessing agreement between two methods of clinical measurement, an incorrect application of this test[1]. Furthermore the correct technique

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has been described only scantily, yielding a study conclusion which is not borne out by the described data analysis.

It is well known that correlation is a poor measure of agreement between two methods of clinical measurement for the following reasons[1]:

1. The correlation coefficient measures the strength of the relationship between the results by the two methods, not whether they agree.
2. A set of measurements which cluster closely around any line (as would occur if one method were to produce results at a mean of 25 per cent of the values given by the other) will result in a high correlation coefficient.
3. As the methods have been developed to measure the same quantity, it would be surprising if they were not related. The test of significance is irrelevant to the question of agreement.

These points are borne out by scrutiny of *Figures 5a, b* and *c* which, despite displaying good correlation, show poor agreement between the two techniques in the measurement of all three variables studied. This would have been more obvious if 95 per cent confidence intervals had been provided for both the limit of agreement lines and for the mean difference to provide an estimate of bias[2] for each measurement method. Without this data it is not possible to comment on the relative precision of each method.

I am also concerned at the non-uniform scatter of data on *Figures 5a* and *b*, there seeming to be a trend of increasing differences between the two methods as the mean value increases. I would like to be reassured that this was quantified, the data tested for normality and if necessary the appropriate transformation applied, otherwise the limits of agreement may be wider apart than necessary for small values and narrower for larger values making the analysis invalid[2].

Finally it would have been helpful to have seen the reproducibility data for the water-filled balloon method as poor agreement between the two methods could have been predicted by seeing a markedly worse set of repeat data with the water-filled balloon probe compared with the air-filled balloon probe.

Therefore though the air-filled microballoon system may well be inexpensive and easy to use, this study has not demonstrated any superiority over the water-filled system both as regards precision of measurement and reproducibility. The claimed advantages of this new technique remain to be proven.

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Statistical comparison of two methods of clinical measurement

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The comparison of two measurement techniques, neither of which can be regarded as being a 'gold standard', is fundamental to much basic research. This apparently simple problem raises many statistical difficulties, which are reviewed in this paper in the context of anorectal manometry. It is concluded that a recently developed approach focusing on the agreement between the two techniques is far superior to the more conventional approach based on correlation. However, until the benefits of the new analysis are more widely recognized (and it is hoped that this paper is a step towards that goal), it is argued that it is useful to present both analyses in such comparisons of measurement techniques.

Keywords: Measurement, anorectal manometry

It is a very common statistical problem to compare two measurement techniques when neither can be regarded as being a 'gold standard'. The approach which is found most commonly in the literature is to apply both measurement techniques to a series of individuals and to plot the two sets of measurements against each other. This might then be accompanied by a correlation coefficient or a regression equation together with the corresponding P value[1,2].

This approach has severe statistical limitations, with the fundamental problem being that correlation measures association rather than agreement. If, for example, one technique consistently gives values which are 50 per cent higher than those of the other technique, then there would be perfect correlation ($r = 1$) but poor agreement. A secondary problem with the use of the correlation coefficient is that it is very sensitive to the range over which the data are recorded. If two different instruments were used to measure systolic blood pressure in a sample of individuals whose 'true' pressures ranged between 130 and 140 mmHg, then it would be most unlikely that a high correlation would be obtained. If the same instruments were compared with a sample of individuals whose true pressures ranged between 100 and 200 mmHg, it would be almost inevitable that a high correlation would result. Thus the correlation coefficient has more to do with the design of the experiment than with the instruments themselves.

Recognizing these problems, Bland and Altman[3] have proposed a much better statistical approach to such comparisons, based on the discrepancy between the two instruments when applied to the same individual. They argue that the distribution of these differences should be examined over a sample of individuals. It is hoped to find the differences clustered around zero, with little variability. If the differences are clustered around a value other than zero, then this indicates that one instrument consistently reads higher than the other. Such a bias, if recognized, is not necessarily too serious, because the readings could be 'corrected' to give better agreement. What is important is the variability; indeed the variability of the sample of differences is the measure of (lack of) agreement which Bland and Altman propose[3]. Further useful information can be obtained by looking at the variability of the differences in relation to the underlying measurement, which might detect, for example, a situation where there was a tendency for a poorer agreement to be found at higher values.

In a recent report in *The British Journal of Surgery*[4], Miller

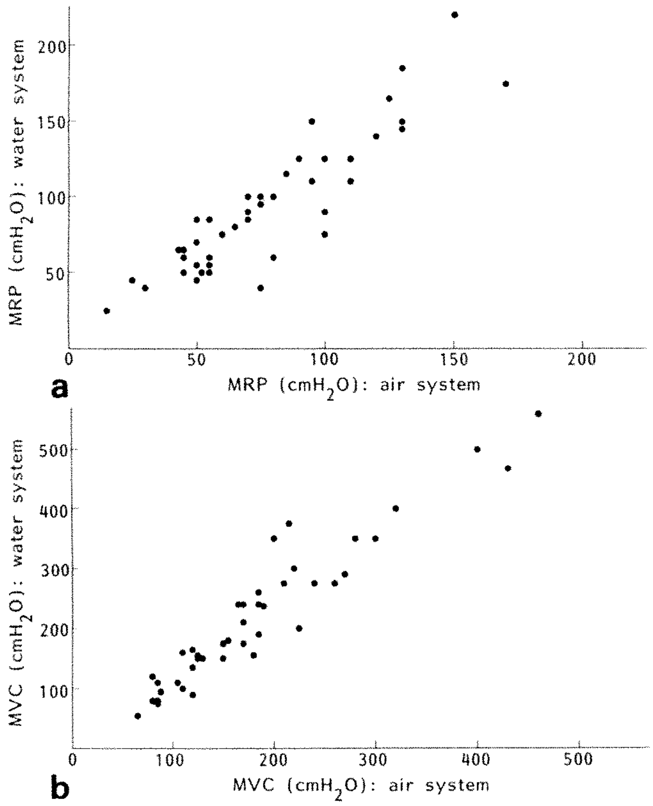

Figure 1 *Plots of* **a** *maximum resting pressure (MRP) and* **b** *maximum voluntary contraction pressure (MVC) with the two measuring systems*

et al. reported the results of a comparison of two manometric systems for use in anorectal physiology, a conventional water-filled system and a 'new' air-filled system. The results were presented in two ways, by the conventional approach of plotting the measurements from the two systems against each other, and the approach advocated by Bland and Altman. The latter analysis has been criticized on two accounts[5,6], first because there were errors in the figures presenting the results of the analysis, and second because the plots from the Bland and Altman analysis revealed certain patterns which were felt to justify further analysis. In this paper we present such an analysis of these data, as a case study in the statistical comparison of two methods of measurement.

Patients and methods

Full details of the study are given in Miller *et al.*[4]. Briefly, a total of 44 individuals was studied using two different instruments, a standard water-filled device and a new air-filled device. The measurements which were taken were sphincter length, maximum resting pressure (MRP) and maximum voluntary contraction pressure (MVC) using the station pull-through technique.

In the original report[4] reproducibility data were obtained for 15 patients using the air system, and for the purpose of this paper comparable data have been obtained for 10 patients using the water system.

In this report we concentrate on MRP and MVC. The sphincter lengths were only measured to the nearest 0·5 cm, which means that the data do not lend themselves to graphical presentation. Moreover, the results of the comparison of the devices in the measurement of sphincter length are clearly apparent in Miller *et al.*[4].

The data are presented using a 'conventional' correlation analysis, based on the Spearman rank correlation coefficient, and by the technique described by Bland and Altman[3], where, for each of the individuals, the difference between the readings for the two instruments is plotted against the mean of the two readings. In addition, the Bland and Altman analysis was repeated with the data transformed to a logarithmic scale.

Results

The Spearman rank correlation coefficient between the two techniques for MRP and MVC was 0·86 and 0·94 respectively (*Figure 1*).

In the Bland and Altman analysis (*Figure 2*), the mean discrepancy between the two instruments for MRP was $-16\,\mathrm{cmH_2O}$ (95 per cent confidence interval -22 to $-10\,\mathrm{cmH_2O}$), i.e. on average, the air-filled system under-read by $16\,\mathrm{cmH_2O}$ relative to the water-filled device. The 95 per cent normal range (i.e. mean ± 2 standard deviations) for the discrepancy in MRP was -56 to $24\,\mathrm{cmH_2O}$. The corresponding figures for MVC were $-36\,\mathrm{cmH_2O}$ (95 per cent confidence interval -49 to $-22\,\mathrm{cmH_2O}$), with a 95 per cent normal range of -121 to $50\,\mathrm{cmH_2O}$.

However, both *Figures 2a* and *b* reveal patterns which suggest that the discrepancy between the two systems is related to the underlying measurement, with a tendency for there to be a larger discrepancy with larger measurements, implying that the figures quoted above for the bias and normal range are not the most appropriate summaries of the relative performance of the instruments.

Analysing the data on a logarithmic scale (*Figure 3*) gives more satisfactory plots. For MRP, there is no suggestion that either the bias or the variability depend upon the underlying measurement. For MVC, there is still a suggestion that the bias increases with the underlying measurement, but this is greatly reduced relative to the original plot, and also the variability is more stable on this transformed scale.

Working on a logarithmic scale corresponds to looking at ratios rather than absolute differences and, converting back to the original scale, it is possible to express the results in terms of percentage differences. This particular transformation is the only one in this context which allows an easy interpretation in terms of the original measurements, but it is remarkable how frequently it is useful in practice. For MRP, the air reading was on average equal to 83 per cent of the water reading (95 per cent confidence interval 78 to 89 per cent), with a 95 per cent normal range of 52 to 133 per cent. For MVC, the corresponding figures were 86 per cent (95 per cent confidence

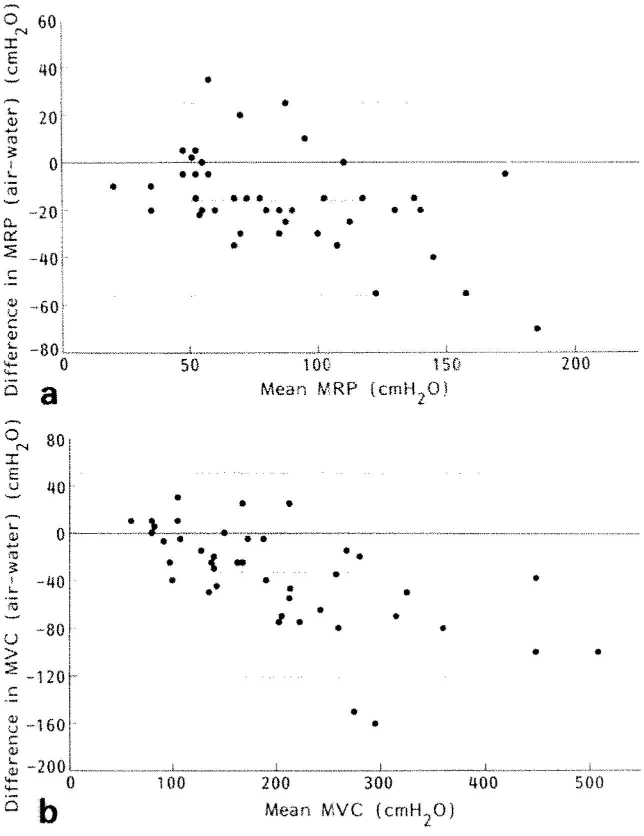

Figure 2 *Plots of* **a** *maximum resting pressure (MRP) and* **b** *maximum voluntary contraction pressure (MVC), relating the discrepancy between the two measuring systems to the underlying measurement. The dashed lines indicate the mean bias and the 95 per cent normal range for the discrepancy between the two instruments*

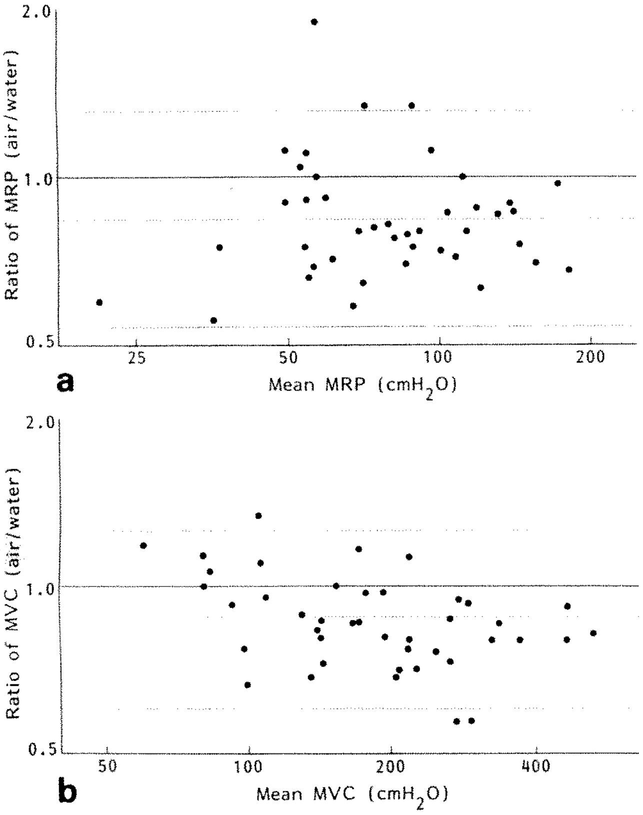

Figure 3 *Plots of* **a** *maximum resting pressure (MRP) and* **b** *maximum voluntary contraction pressure (MVC), relating the ratio of the two results to the underlying measurement. The dashed lines indicate the mean bias and the 95 per cent normal range for the discrepancy between the two instruments*

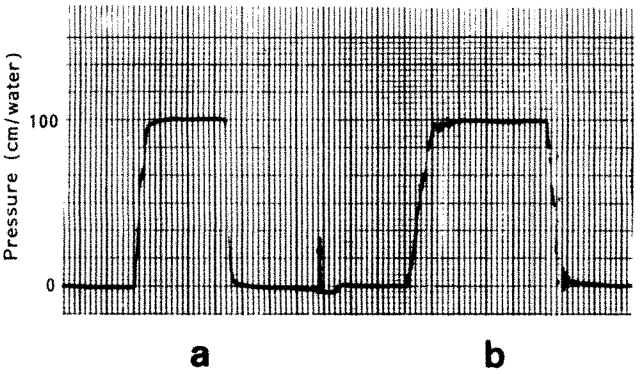

Figure 4 *Trace of pressure change when calibrating the water-filled system.* **a** *using the pressurized chamber that was used to calibrate the air-filled system and* **b** *by raising the catheter to the same pressure, 100 cm/water. Identical pressures were recorded*

interval 82 to 92 per cent), with a 95 per cent normal range of 59 to 126 per cent.

Bland and Altman plots of the raw data from the two reproducibility studies revealed no systematic trends. The standard deviations of the differences between replicate measurements of MRP were 16·4 and 5·0 cmH$_2$O for the water and air systems respectively. The corresponding results for MVC were 37·0 and 10·7 cmH$_2$O.

It has been suggested that differences in calibration might explain the discrepancies observed between the two instruments[6]. *Figure 4* shows the calibration of the water-filled system by both the standard method of raising the catheter balloon to 100 cm above zero (100 cm/water) and the same pressure using a pressurized chamber connected to a mercury sphygmomanometer that was used to calibrate the air-filled balloon. The same pressure is accurately recorded, indicating, as expected, that differences in the method of calibration cannot account for any differences in the pressure recorded when in use clinically.

Discussion

The relatively high correlation between the results for the two instruments is no more than would be expected in such a comparison, and indeed it is difficult to conceive of a sitation where the readings of two devices claiming to measure the same parameter were not associated! It is necessary however to demonstrate that such an association exists if one is trying to introduce a new technique which purports to measure the same parameter as the old, and, until the Bland and Altman approach is more firmly established in the clinical literature, we would argue that such a plot is a useful addition to the Bland and Altman plot. Seen in isolation, it can obviously be seriously misleading. Seen together with the Bland and Altman plot, it would, we believe, help many clinicians to reach appropriate conclusions about their data. Approaches such as those advocated by Bland and Altman, with all of their sound statistical advantages, tend to be viewed with suspicion by clinicians. At least in our application the 'conventional' plot does quickly convey the message that the two instruments are measuring much the same phenomenon, which is essentially all that was claimed by Miller *et al.*[4].

The Bland and Altman plots with even the raw data show that there can be very large discrepancies between the two instruments, with clear evidence of a systematic bias, and, more seriously, unacceptable variability. The trend seen in these plots of variability increasing with the underlying measurement pointed to a logarithmic transformation, allowing the final results to be expressed in terms of percentage variability. However the data are analysed, they are clearly consistent with the conclusion of Miller *et al.*; 'The differences between the recorded pressures, however, did mean that the two systems could not be interchanged, and therefore any longitudinal study would require the exclusive use of one or other technique.'[4].

The data as presented above give no insight into which of the two manometry systems is to be preferred in terms of precision of measurement. There is no 'gold standard' against which any system can be compared and therefore such an assessment is impossible.

There are several reasons for the lack of agreement. The water-filled system has inferior reproducibility compared with the air-filled system and, as stated in the original paper, the larger diameter of the water-filled microballoon will inevitably result in a higher pressure being recorded. In addition the air-filled system measures pressure over a zone (1 cm) as compared with the more discrete measurement of the water-filled balloon. This difference in balloon shape is probably responsible for the better reproducibility of the air-filled system as it measures the integrated pressure over the zone and is less liable to be affected by small differences in position.

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Role of duplex scanning in the selection of patients for carotid endarterectomy

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A retrospective review of 63 patients undergoing duplex scanning and angiography for suspected carotid artery disease was performed to evaluate the need for routine angiography before carotid endarterectomy. A consultant surgeon (M.H.) made a simulated management decision on the basis of a clinical summary and a duplex scan report. Twenty-four patients were selected for surgery without angiography; duplex scanning had a sensitivity of 100 per cent and a specificity of 90 per cent in the detection of internal carotid artery stenosis. In two cases duplex scanning misdiagnosed a total occlusion as a critical stenosis. Eighteen patients failed to meet the criteria for surgery and were referred for angiography. Twenty-one patients were selected for conservative treatment on the basis of the duplex scan report. Combining the surgical and conservative groups (45 patients), duplex scanning had a sensitivity of 96 per cent and specificity of 95 per cent for the detection of stenosis greater than 50 per cent. In the identification of a total occlusion, duplex scanning had a poor sensitivity of 50 per cent. These results suggest that routine angiography before carotid endarterectomy is unnecessary in selected patients but that a suspected occlusion should be confirmed by angiography.

Keywords: Duplex scanning, carotid artery disease, endarterectomy, angiography, surgery, ultrasonography

The traditional method of preoperative assessment of carotid artery disease is contrast radiography[1]. Of three techniques currently in use, conventional arteriography and intra-arterial digital subtraction arteriography give excellent views of the carotid tree but require selective carotid catheterization with well documented morbidity and mortality[1,2]. Intravenous digital subtraction angiography, on the other hand, has a lower complication rate but in many cases provides suboptimal views of the carotid bifurcation and of the distal vessels[3,4].

In recent years duplex scanning has proved highly accurate in identifying significant carotid stenoses[5–8], and in addition has definite advantages over angiography. It is non-invasive and therefore repeatable, and in characterizing the carotid plaque provides more information than is available from other methods[9]. It is understandable therefore that duplex scanning should stimulate a reassessment of the need for routine angiography before endarterectomy[10,11].

After several years of experience with duplex scanning, this study was carried out to evaluate its role in the preoperative assessment of carotid artery disease.

Patients and methods

This study is retrospective and all patients were managed by conventional methods.

The clinical records and duplex scan reports of 63 patients undergoing both duplex scanning and arteriography over a 2-year period for suspected carotid artery disease were reviewed. All scans were performed by one experienced ultrasonographer (S.E.A.C.) who performs over 500 scans per year. The scanner in all cases was an ATL 600 MK 5® (Advanced Technology Laboratories UK Ltd., Letchworth, UK) using a 5 MHz probe for the Doppler signal and a 7·5 MHz probe for the B-mode image. A standard examination technique and standard criteria for the assessment of stenosis[12] were used.

A summary of the clinical details of each patient and the scan report were presented to a consultant vascular surgeon (M.H.) who had no knowledge of the result of the arteriogram, and he selected patients for: (1) surgery without angiography; (2) angiography; or (3) conservative treatment. The criteria for surgery without angiography were: a technically satisfactory scan, a clear history of hemispheric symptoms, a lesion appropriate for symptoms, and a stenosis greater than 50 per cent (in diameter) but not occluded. Arteriograms were then reviewed for each group by a consultant radiologist (W.D.J.), with stenosis being calculated as the percentage reduction in diameter compared with normal distal internal carotid artery. In addition, careful note was made of disease in the proximal common carotid and the carotid siphon, and the carotid bifurcation was assessed for the presence of ulceration.

Results

Sixty-three patients (126 carotid systems) were reviewed. There were 49 men and 14 women, mean age 61 years (range 31–78 years). Symptoms were as shown in *Table 1* and were predominantly hemispheric. Eleven per cent of duplex scans were unsatisfactory because of equipment failure, anatomical variations such as a high carotid bifurcation or very deep or superficial arteries, calcification in the atheromatous plaque or tortuosity of vessels which prevented adequate imaging of the bifurcation. Two patients (3 per cent) had transient neurological events during arteriography, both recovering within 24 h. Of the 63 patients, five (8 per cent) had minor disease in the proximal common carotid arteries, and seven (11 per cent) had minor siphon disease on arteriography. No patient had severe proximal or siphon stenosis. One patient had a cerebral tumour which was diagnosed on cerebral computed tomography scanning.

Results of vascular surgical screening

Selected for surgery without angiography. Twenty-four patients were selected for operation (20 men, four women). Of 48 carotid arteries in this group, three non-symptomatic vessels had unsatisfactory scans. Of the remaining 45 vessels, 41

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Table 1 *Range of symptoms in 63 patients with suspected carotid artery disease*

Symptom	No. of patients
Nil	3
Amaurosis fugax	22
Transient ischaemic attack	23
Stroke	6
Global ischaemia	9

(91 per cent) were correctly diagnosed, and in four there was disagreement between scan and arteriogram.

Two vessels diagnosed by duplex scanning as critically stenosed were totally occluded, and surgery would have been inappropriate. In one, a plaque which was ulcerated and 40 per cent stenosed on angiography was diagnosed as a 50 per cent stenosis by duplex scanning. This patient had multiple episodes of amaurosis fugax and went on to endarterectomy. In the other patient the error was made by angiography, when an arch injection after failure of selective catheterization produced poor quality films which missed a stenosis. This patient also had a successful endarterectomy.

Of these 24 patients, all but four have undergone operation. Two patients with occlusions were treated conservatively, as were two other patients who, while being correctly assessed by duplex scanning, were not referred for surgery.

Selected for angiography. Eighteen patients did not fulfil the criteria for surgery and were referred for angiography and conventional management.

Selected for conservative treatment. The remaining 21 patients (16 men, five women) were selected for conservative treatment on the basis of duplex scanning without angiography. The status of 94 per cent of carotid arteries was accurately diagnosed. There was disagreement between scan and arteriogram in two arteries. In one vessel, a critical stenosis on arteriography was deemed an occlusion by duplex scanning, and in another patient a 60 per cent stenosis on arteriography was assessed at 40–50 per cent by duplex scanning. This last patient was treated conservatively. Three patients in this group did in fact have an endarterectomy. One was the patient with critical stenosis. The two others were patients for whom there was close agreement between scan and arteriogram but, because they were under the care of a surgeon with different indications for carotid endarterectomy, they underwent operation.

When the operation and conservative groups were combined, assessing both symptomatic and contralateral carotid arteries, there was a sensitivity of 96 per cent and specificity of 95 per cent for the detection of stenosis greater than 50 per cent. There was, however, a sensitivity of 50 per cent and specificity of 95 per cent for the detection of total occlusion. Duplex scanning was not reliable in the detection of ulceration. In the operation and conservative groups there were 25 ulcers seen angiographically, but only 13 (52 per cent) of these were diagnosed by duplex scanning, giving a sensitivity of 44 per cent and specificity of 96 per cent.

Discussion

Arteriography has been considered essential before endarterectomy, the gold standard being selective carotid studies with views in three planes[13]. With both conventional arteriography and intra-arterial digital subtraction arteriography, however, serious neurological complications have been reported in up to 5 per cent of cases[1,2,14–16], and even higher in some prospective studies, with a low but definite mortality rate. The complication rate of the investigation, therefore, approaches that for the operation[17]. By contrast, the combination of duplex scanning with intravenous digital subtraction angiography offers safety, with visualization of the carotid bifurcation in approximately 90 per cent of cases. However, these views may be inadequate for the assessment of ulceration and the distal vessels. Non-invasive studies, and particularly duplex scanning, have become very accurate in recent years with sensitivities and specificities of greater than 90 per cent for the detection of carotid stenosis[5–8]. Increasingly, the need for routine angiography has been questioned and over 200 endarterectomies without angiography have been reported in selected patients without complication[10,11,18–23].

Although this study was retrospective, the decision to operate was made without knowledge of the arteriogram, and in this carefully selected group of patients a high degree of accuracy was found for the detection of significant disease by duplex scanning. No significant lesions were missed. This suggests that a significant proportion of patients may be undergoing unnecessary arteriography if duplex scanning has excluded significant disease. It is important to note that we have compared duplex scanning with selective triplanar arteriography which is more accurate than biplanar views of the carotid bifurcation[13], and our comparison, therefore, is with the most accurate method of angiography currently available. We support the policy of endarterectomy without angiography in selected cases but certain prerequisites need to be stressed.

Firstly, such a policy needs to be based on experience and a proven track record of non-invasive assessment, such as demonstrated by this study. Examinations should be performed by an experienced ultrasonographer in a standardized manner utilizing both B-mode imaging and spectral analysis, and using accepted criteria for the assessment of stenosis. In addition, careful note should be taken of abnormal pulsatility of either the distal internal or proximal common carotid artery, or of mismatch between the apparent stenosis on spectral analysis and the visible plaque, as these factors may indicate disease outside the cervical carotid system. The report should state whether the scan is technically satisfactory and set confidence levels for the assessment of stenosis.

We believe the following criteria for the selection of patients for operation without angiography have proved valid in this study.

Clear hemispheric symptoms

Non-hemispheric or global symptoms are more likely to be the result of disease outside the carotid bifurcation, and angiography should be performed. Ideally a cerebral computed tomography scan should be performed on all patients who do not have angiography to exclude the rare cases with intracerebral disease, such as primary and secondary tumour deposits.

A satisfactory scan

The 11 per cent of unsatisfactory scans in this series is comparable with that reported by others[24]. Scans may be unsatisfactory because the bifurcation is high, or vessels are very superficial or very deep. Calcification in the plaque may prevent adequate visualization of the bifurcation, or tortuosity may make complete insonation of the vessel difficult. A confidence level should be stated by the operator for all scans, and where this is below a set limit, angiography should be recommended.

A lesion appropriate for symptoms

The lesion should be in the appropriate internal carotid artery and should be surgically accessible.

Stenosis greater than 50 per cent

It is well recognized that hemispheric symptoms can be due to ulcerated plaque with less than 50 per cent stenosis[25,26]. However, while others have reported good results in the detection of ulceration by duplex scanning[27], that has not been our experience. In this study only 40 per cent of angiographically detected ulcers were seen on duplex scanning. While a correlation of duplex scanning with operative findings may give better results, this comparison needs to be assessed prospectively, and it is wiser to perform angiography.

The main concern about operating without angiography relates to undetected proximal or distal disease. The reported incidence of siphon disease varies widely, from 6 to 80 per cent of patients undergoing angiography[1,28], and was 11 per cent in this series. The evidence for the importance of siphon disease is conflicting. While some believe that severe siphon stenosis may increase the risk of endarterectomy[25,28], others maintain that siphon disease does not affect perioperative stroke rate or outcome[27,29]. Our experience is that the presence of siphon disease need not influence management unless a critical siphon stenosis is present and this should be evident from mismatch between the B-mode image and the Doppler signal. Severe proximal disease is rare and again should be evident from the duplex scan.

Differentiation of a critical stenosis from an occlusion is often difficult and duplex scanning was unreliable in this context. However, it should be stressed that in each case of misdiagnosis the scan report recognized the possibility of error. The difficulty lies with plaques where the flow distal to the stenosis is so sluggish or confined to such a narrow jet that detection by the scanner is difficult. These cases are uncommon but, while O'Donnell *et al.*[9] and others have reported greater accuracy in detecting occlusions and have suggested that arteriography may be avoided in these cases, we believe that all 'occlusions' should be confirmed by angiography to avoid missing a critical stenosis amenable to surgery.

In summary, duplex scanning is reliable and reproducible in the diagnosis of carotid artery disease. It is non-invasive, cost effective and repeatable. In certain highly selected cases it provides enough information for safe carotid endarterectomy without angiography, a practice now adopted for all patients in whom the ultrasonographer is confident of the diagnosis and for whom the symptoms fit with the ultrasound findings. Excluding suspected carotid occlusions, angiography did not alter management in any of the cases reported. Furthermore, duplex scanning proved reliable in excluding significant carotid disease and can therefore prevent unnecessary angiography.

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Non-invasive estimation of peripheral resistance using Pulse Generated Runoff before femorodistal bypass*

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The measurement of peripheral resistance (PR) is a useful technique for predicting the outcome of femorodistal bypass. In an attempt, non-invasively, to predict PR, Pulse Generated Runoff (PGR) was used to assess 35 consecutive patients undergoing femorodistal non-reversed vein bypass for critical ischaemia. The PGR subscores (anterior tibial, posterior tibial, peroneal, pedal arch status were correlated against the measured PR. Using multiple linear regression three resistance values were derived for runoff at different levels: (1) a single calf vessel (R1); (2) distal popliteal artery (R3); (3) irrespective of the level (R0). There was good agreement between the predicted resistances R0, R1 and R3 and the measured PR. In the single calf vessel group (R1) the limits of agreement (−0·41 to +0·39) and 95 per cent confidence interval (−0·16 to +0·14) with the measured PR were better than in the R0 and R3 groups. These levels of agreement are small enough to replace the measured PR with the predicted PR method. Using the appropriate resistance equation in a further prospective series of 14 cases, there was agreement between the predicted and measured PR (limits of agreement −0·67 to +0·41; 95 per cent confidence interval −0·26 to +0·15). These results confirm the value of PGR in the assessment of critically ischaemic limbs particularly with a single calf vessel. Calf vessel continuity with the pedal arch appears to be a major determinant of PR, particularly in the isolated calf vessel group. A non-invasive resistance value can be derived which will predict the intraoperative peripheral resistance and should help predict subsequent graft outcome.

Keywords: Peripheral resistance, femorodistal bypass, critical ischaemia, Pulse Generated Runoff

Conventional preoperative arteriograms and Doppler ultrasonography are routinely used in the evaluation of patients with critical ischaemia[1–8]. In addition to the usual criteria, patients are selected for femorodistal surgery on the basis of an adequate run-off. In particular, calf vessel continuity with the pedal arch appears to be an important factor in early graft patency[9–12].

Conventional arteriography provides limited visualization of both distal calf vessels and pedal arches, especially in the presence of severe proximal disease. With the availability of intra-arterial digital subtraction arteriography better calf vessel resolution has been achieved with a lower contrast load, but in severe ischaemia contrast dilution and movement artefacts may cause some patent distal vessels to be missed. In an attempt to predict the outcome of femorodistal bypass various arteriographic scoring systems have been devised, ranging from the simple to the complex[3,4,7,13]. Despite the complexity of the scoring systems there remains a group of patients in whom the scoring systems fail to predict successful grafts. Pre-bypass operative arteriography improves vessel resolution by avoiding the problem of contrast dilution distal to a stenosis[14,15]. Despite the improved visualization, pre-bypass operative arteriography fails to provide any functional information about the run-off and does not allow surgery to be planned.

Doppler ankle systolic pressures and ankle/brachial indices are useful in assessing the severity of disease, but are unable to predict the outcome of femorodistal bypass[5,6,16].

Careful Doppler examination of the ischaemic foot in the dependent position may help identify patent vessels not seen on arteriography[17,18]. Quantification of these signals by waveform analysis, including pulsatility index[19], Laplace transform[20] and principal component analysis[21], are not applicable, as the distal waveforms are often severely damped.

Pulse Generated Runoff (PGR)[22] overcomes the problem of damped distal Doppler signals as a new pulse wave is generated by rapid inflation of a sphygmomanometer cuff wrapped tightly around the upper calf. Augmented flow can then be detected at the ankle if the calf vessel is patent. Recent studies have reported a good correlation between the PGR score and peripheral resistance (PR) and subsequent outcome following femorodistal bypass[22,23].

The measurement of PR at the time of calf vessel exploration and on completion of the distal anastomosis has been shown to correlate with successful femorodistal grafting[24–28]. The aims of this study were (1) to derive non-invasively a measure of PR and (2) to compare this with PR measured at the time of surgery.

Patients and methods

Thirty-five consecutive patients (25 men, 10 women) undergoing non-reversed vein femorodistal bypass for critical ischaemia were studied. Their median age was 70 years (range 54–86 years). Twenty-two grafts were performed to the distal popliteal artery, three to the tibioperoneal trunk and ten to a single calf vessel. All patients underwent non-invasive assessment before surgery, including ankle pressures and a PGR study. An intra-arterial digital subtraction arteriogram was obtained in all cases.

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Pulse Generated Run-off

Before the PGR study the patient was rested for 10 min with the legs dependent, then placed in a supine position with the heels resting on a support. An inflatable cuff was wrapped tightly around the upper calf. This was rapidly inflated and deflated to a pressure of 300 mmHg at 50 cycles per min. The anterior tibial, posterior tibial and peroneal arteries were assessed at the ankle. Each vessel was scored out of 2 (0, no signal; 1, monophasic; and 2, biphasic waveforms), giving a maximum score of 6 for each leg (*Figure 1*). The dorsal pedal arch (lateral tarsal, dorsalis pedis and arcuate arteries) was mapped using the PGR system. Calf vessel continuity with the pedal arch was determined by combining PGR with the pedal arch patency test of Roedersheimer *et al.* (*Figure 2*)[29]. For each vessel in continuity with the arch an additional point was given (pedal arch status (ARCH) score = 0–3). The total PGR/ARCH score was 9 for each leg. Thus for each leg there were two scores, one for PGR (0–6) and another for PGR/ARCH (0–9).

Operative measurement of peripheral resistance

The PR was measured at the site chosen for the distal anastomosis. A newly developed end tapered soft 6/8 Fr catheter (Portex®, Portex Ltd., Hythe, UK) was introduced through an arteriotomy (*Figure 3*). An infusion of heparinized blood was made at a physiological pressure of approximately 80–100 mmHg. Pressure (P) was measured by a pressure transducer and flow (Q) by a Doppler flowmeter[30]. Simultaneous recordings of pressure and flow were converted by an Apple 2E (Apple Computer Company, Cupertino, California, USA) microcomputer into peripheral resistance units.

Statistics

The comparison between the PGR, PGR/ARCH scores and the measured PR were evaluated statistically using the Spearman rank (r_S) correlation test with a significance level of $P<0{\cdot}05$. Multiple linear regression analysis was used to derive a predicted resistance value. The independent variables, PGR subscores for the anterior tibial, posterior tibial, peroneal and pedal arch, were correlated against the dependent variable, PR. A series of equations was derived which best described the relationship between the non-invasive PGR assessment of the calf vessels and the measured PR. The predicted PR was then compared with the measured PR using measurement of agreement, described by Bland and Altman[31], rather than correlation coefficients, as the latter do not reflect agreement between the two methods of PR measurement. In this situation the null hypothesis is that neither method is linearly related. The probability of this is small and so a high correlation does not reflect agreement.

Results

Measured peripheral resistance

There was a reasonable correlation between the PGR score and the measured PR for all 35 grafts ($r_S=-0{\cdot}39$; $P<0{\cdot}02$) (*Table 1*). The correlation improved with the addition of the ARCH score (PGR/ARCH), ($r_S=-0{\cdot}44$; $P<0{\cdot}01$). In the distal popliteal

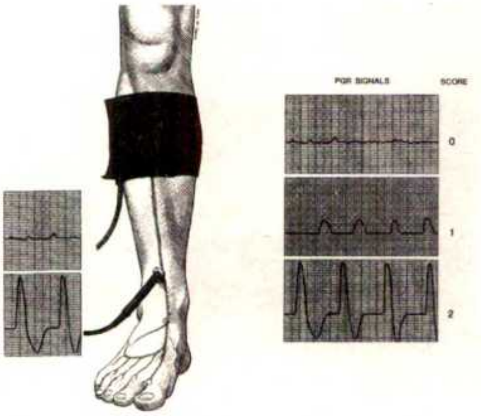

Figure 1 *Pulse Generated Runoff assessment. This shows a 10 MHz Doppler pencil probe insonating the anterior tibial artery. The top trace shows a non-pulsatile Doppler signal and below the Pulse Generated Runoff (PGR) augmented flow wave. On the right are three Doppler traces, absent, monophasic and biphasic, with the appropriate scores* (Br J Surg 1989; **76**: 1202–6)

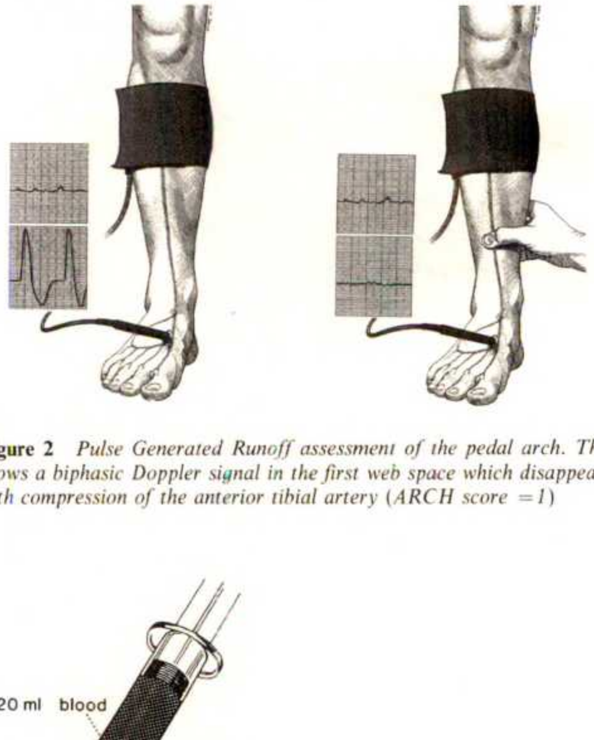

Figure 2 *Pulse Generated Runoff assessment of the pedal arch. This shows a biphasic Doppler signal in the first web space which disappears with compression of the anterior tibial artery (ARCH score = 1)*

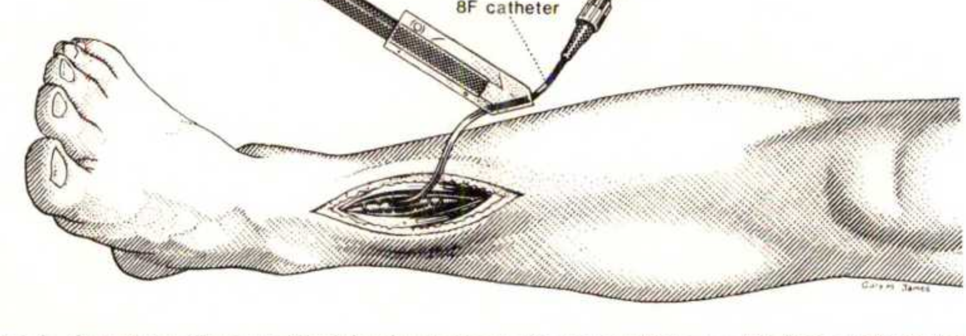

Figure 3 *Operative measurement of peripheral resistance in the anterior tibial artery* (Br J Surg 1989; **76**: 1202–6)

group, PGR failed to correlate with the measured PR (*Table 1*), reflecting the inability of PGR to recognize proximal calf vessel disease. In the single calf vessel group there was a significant correlation between the PGR score and the measured PR ($r_S = -0{\cdot}69$, $P < 0{\cdot}025$). This improved with the addition of the ARCH score ($r_S = -0{\cdot}88$, $P < 0{\cdot}001$).

Predicted peripheral resistance

Using multiple linear regression the PGR calf vessel scores for the anterior tibial, posterior tibial and peroneal and the ARCH score were correlated against the measured PR. Three PR values were derived at different sites: (1) a single calf vessel (R1); (2) distal popliteal artery (R3); and (3) irrespective of the level (R0) (*Table 2*). There were insufficient numbers to analyse in the tibioperoneal artery group (*Appendix* and *Figure 4*).

Table 1 *Pulse Generated Runoff and Pulse Generated Runoff/pedal arch status scores correlated against the measured peripheral resistance*

	Correlation PR	Overall ($n=35$)	Distal popliteal ($n=22$)	Single calf vessel ($n=10$)
PGR	r_S	−0·39†	−0·07*	−0·69†
PGR/ARCH	r_S	−0·44†	−0·08*	−0·88‡

PR, peripheral resistance; PGR, Pulse Generated Runoff; ARCH, pedal arch status; r_s, Spearman rank correlation; *, not significant; †, $P<0{\cdot}01$; ‡, $P<0{\cdot}001$

Table 2 *Level of agreement between the predicted peripheral resistance and the measured peripheral resistance*

	R0 ($n=35$)	R1 ($n=10$)	R3 ($n=22$)
Mean difference	−0·01	0·01	−0·007
+2 s.d.	0·81	0·39	0·59
−2 s.d.	−0·83	−0·41	−0·60
95 per cent confidence interval	−0·15–+0·13	−0·16–+0·14	−0·14–+0·126

R0, irrespective of the level of distal anastomosis; R1, single calf vessel; R3, distal popliteal; s.d., standard deviation

The use of multiple linear regression to derive a predicted PR resulted in a better correlation with the measured PR than with the PGR and PGR/ARCH scores, especially in the distal popliteal group ($r_S = -0{\cdot}07$, $P > 0{\cdot}05$ to $r_S = 0{\cdot}57$, $P < 0{\cdot}001$). The improved linear relationship may be in part due to the variable weighting of the calf vessels. At this level, the anterior tibial artery and the state of the pedal arch appear to be the major determinants of PR rather than all three calf vessels equally.

There was good agreement between the predicted resistances R1, R3 and R0 and the measured PR at the time of surgery (*Table 2*). In particular there was a good agreement between the predicted resistance in the single calf vessel group (R1) and the measured PR (limit of agreement −0·41 to +0·39 peripheral resistance units, 95 per cent confidence interval −0·16 to +0·14) (*Figure 5*). In the distal popliteal group (R3), weighting of the individual calf vessels produced a good agreement between the predicted and measured PR (95 per cent confidence interval −0·14 to +0·126) but with wider limits of agreement (−0·60 to +0·59) (*Figure 6*).

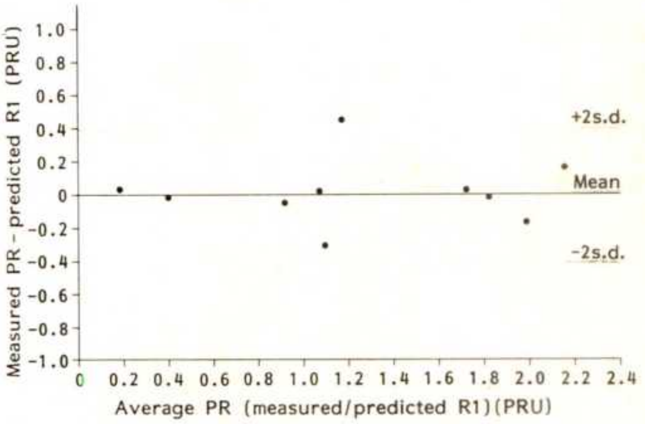

Figure 5 *Level of agreement between the measured peripheral resistance and the predicted resistance (R1), single calf vessel at the time of surgery. PR, peripheral resistance; PRU, peripheral resistance units; s.d., standard deviation*

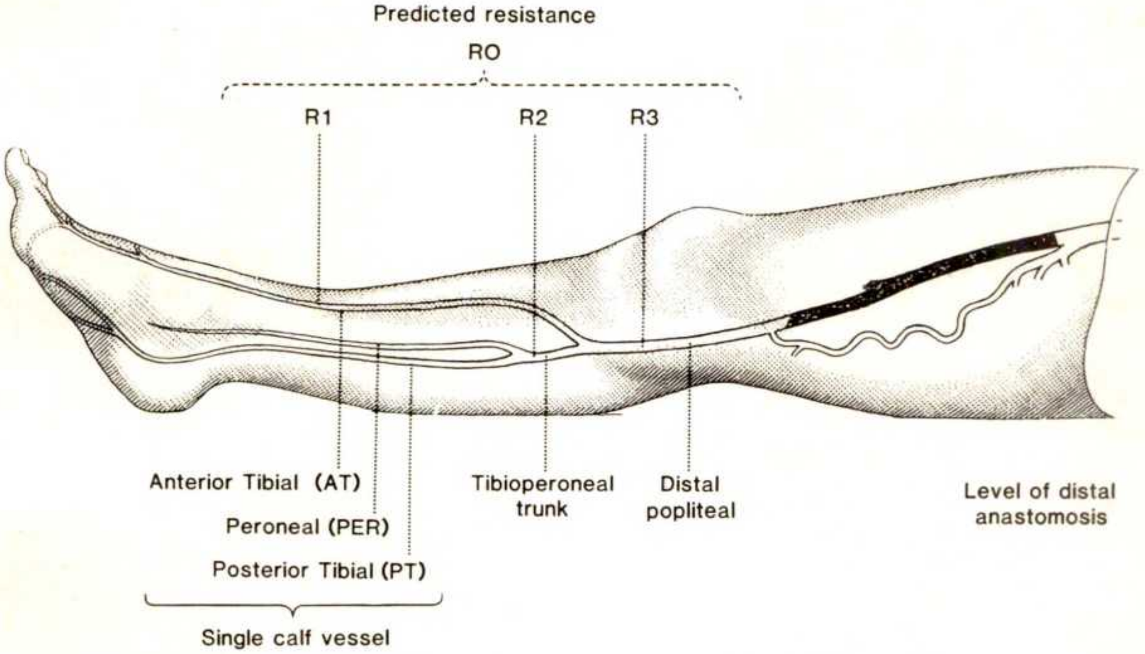

Figure 4 *Predicted peripheral resistance values R0, R1, R2, R3 in relation to the leg*

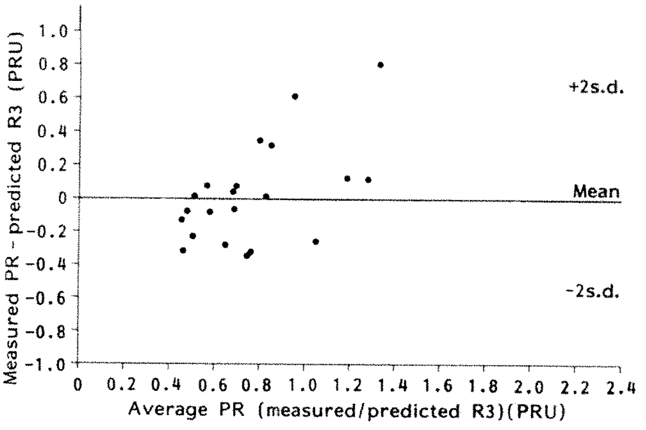

Figure 6 *Level of agreement between the measured peripheral resistance and the predicted resistance (R3), distal popliteal artery at the time of surgery. PR, peripheral resistance; PRU, peripheral resistance units; s.d., standard deviation*

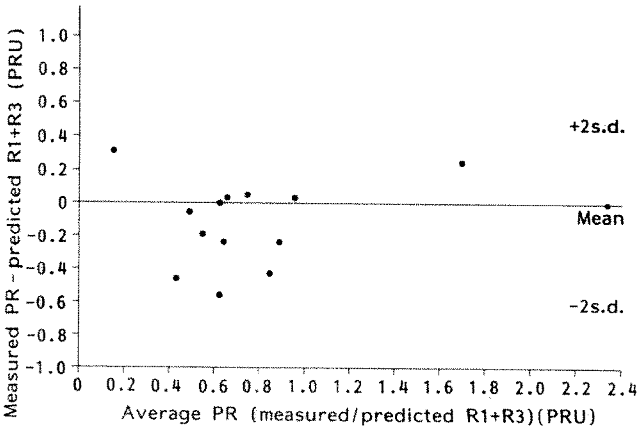

Figure 7 *Level of agreement between the measured peripheral resistance and the predicted peripheral resistance values (R1 + R3) in a prospective series of 14 femorodistal non-reversed grafts. PR, peripheral resistance; PRU, peripheral resistance units; s.d., standard deviation*

Prospective series

The equations R1 and R3 were then validated in a prospective series of 14 non-reversed vein femorodistal grafts. There was good agreement between the predicted and measured PR (95 per cent confidence interval −0·26 to +0·15) (*Figure 7*).

Discussion

The recent trend towards more distal reconstructions has highlighted the inadequacy of conventional arteriography and shown a need for better assessment of distal calf vessels. Failed reconstructions result in higher amputation sites, increased morbidity, mortality, poor quality of life and wasted resources[32-34].

The preoperative prediction of subsequent graft function is usually based upon a combination of arteriographic and ultrasound data[1,2,5-7]. Preoperative transcutaneous oxygen tension and pulse volume recordings have been evaluated, but are of poor predictive value[35,36].

More recently several authors have reported the value of intraoperative PR measurements[23-28]. These appear to be a better predictor of both short and long term graft patency[27,28] than other methods, including arteriography.

Menzoian *et al.* reported that a simple arteriographic scoring system based on the number of patent calf vessels failed to predict the measured PR[37]. More sophisticated scoring systems have graded the severity of calf vessel disease and allowed for the presence of a patent pedal arch and have shown good correlation with the measured PR[3]. In the same study LaMorte used multiple linear regression to derive a predicted resistance based on the arteriographic subscores. In a retrospective study of 39 patients the predicted resistance correlated significantly with the measured PR ($r_S = 0{\cdot}78$, $P < 0{\cdot}001$).

Careful Doppler examination may identify patent calf vessels and pedal arches not seen on conventional arteriography[16,38]. Campbell *et al.* reported that 35 per cent of vessels judged to be occluded on arteriography had normal or damped Doppler signals[38].

PGR generates a new pulse wave which can be detected at the ankle if the vessel is patent. Semiquantitative analysis of the waveform allows a score to be derived for each calf vessel. In this study PGR correlates reasonably well with the measured PR (*Table 1*). The addition of the ARCH score, as with the arteriographic scoring systems, improves the correlation with measured PR. In contrast to arteriography, pedal arch assessment using PGR is easy to perform, repeatable and gives some functional information.

The poor correlation between PGR and PR for the distal popliteal grafts may be attributable to several factors. The PGR cuff was placed at the level of the distal popliteal and tibioperoneal arteries. The augmented flow at the ankle must, therefore, represent calf vessel patency between the cuff and the ankle. Positioning of the cuff above the knee may have allowed proximal calf vessels to be evaluated, but this was not studied. In the below knee position, the PGR system only assesses the individual calf vessels and not their proximal connections.

In the majority of arteriographic scoring systems no account is taken of the relative contributions of each vessel to the overall resistance. Because of the difficulties involved in the visualization of the pedal arches this is often discounted from the score.

In this study PGR was used to assess both calf vessel and pedal arch patency. In an attempt to assess the relative contributions of the calf vessels to the overall PR, multiple linear regression analysis was used. This examines the linear relationship between a dependent variable, PR, and two or more independent variables, e.g. PGR subscores, by determining an equation which best describes the relationship. A series of regression coefficients is derived which weights the independent variables.

In all three equations (R1, R3, R0) the ARCH coefficient appears to be a major determinant of PR. On this basis, continuity between the calf vessel and the pedal arch is clearly an important factor in overall PR. For grafts to a single calf vessel the absence of the arch produces a predicted PR value of greater than 1, which in our experience is rarely compatible with a successful bypass.

In the R0 equation the peroneal artery has a high positive coefficient consistent with a high resistive bed. This finding was previously reported by LaMorte *et al.* who noted that on arteriography the peroneal coefficient approached zero[3]. These results may reflect that in the normal lower leg the peroneal artery does not usually communicate directly with the pedal arch.

In the R1 equation all three vessels (anterior tibial, posterior tibial, peroneal) have similar coefficients. The weighting of the peroneal artery supports the finding that in severe disease, particularly where there is an isolated patent calf vessel, the peroneal artery is often relatively disease free and in continuity with the pedal arches[39,40]. Calf vessel continuity with the pedal arch is an important determinant of PR which has been well correlated with successful femorodistal reconstruction. A non-invasive PR measurement can now be derived from PGR using multiple linear regression which can predict the operative PR. We would recommend that patients be selected for calf vessel exploration on the basis of a PGR and non-invasive PR measurement rather than arteriographic appearance alone. This is a simple, inexpensive, non-invasive test of calf vessel run-off, which can be applied to all patients with critical ischaemia.

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Appendix

Predicted peripheral resistance equations using multiple linear regression analysis:

$$\mathrm{R1} = 2{\cdot}97 - 0{\cdot}90(\mathrm{PT}) - 0{\cdot}57(\mathrm{AT}) - 0{\cdot}63(\mathrm{PER}) - 0{\cdot}77(\mathrm{ARCH})$$

$$\mathrm{R3} = 1{\cdot}46 - 0{\cdot}005(\mathrm{PT}) - 0{\cdot}15(\mathrm{AT}) - 0{\cdot}04(\mathrm{PER}) - 0{\cdot}34(\mathrm{ARCH})$$

$$\mathrm{R0} = 1{\cdot}02 + 0{\cdot}02(\mathrm{PT}) - 0{\cdot}13(\mathrm{AT}) + 0{\cdot}20(\mathrm{PER}) - 0{\cdot}14(\mathrm{ARCH})$$

where R1 = single calf vessel grafts; R3 = distal popliteal grafts; R0 = overall, irrespective of the level of the anastomosis; PT = posterior tibial; AT = anterior tibial; PER = peroneal; ARCH = ARCH Score.

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Femoropopliteal arterial fibrodysplasia

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Fibrodysplasia is a rare and unusual cause of obstruction of the superficial femoral or popliteal artery. Three young patients with intermittent claudication due to occlusion of the femoropopliteal artery are described. Histological examination showed destruction of the elastic and muscle fibres of the media. In one patient secondary fibrosis of the intima was seen. The adventitia showed an increase in elastin fibres in all cases. The lesions described can be respectively classified as perimedial fibroplasia, as medial dissection and as intimal fibroplasia. This is the first description of a patient with histopathologically proven perimedial fibroplasia and medial dissection of the femoropoliteal artery and the second case of intimal fibroplasia.

Keywords: Fibromuscular dysplasia

Most obstructions in the femoral and popliteal vessels are due to atherosclerotic occlusive disease. Popliteal artery stenosis can also be due to entrapment by the gastrocnemius muscle or adventitial cystic disease[1]. Fibrodysplasia is a known cause of obstruction of the renal artery. Less frequently it is seen in the carotid, visceral, vertebral, axillary or iliac arteries, but it is a rare and unusual cause of stenosis of the femoral or popliteal arteries[2,3]. This article describes three young patients with intermittent claudication due to femoropopliteal occlusive disease. Microscopic examination of the diseased arteries showed dysplastic disease. The different types of dysplastic disease and their aetiological factors and angiographic appearances are discussed.

Patients and methods

Case reports

Case 1. A 15-year-old girl presented with disabling claudication in the right leg. The claudication existed for more than a year. There was no rest pain. The patient did not smoke. On physical examination there were normal pulsations over the femoral arteries and over the left pedal arteries. There were no pulsations over the right pedal arteries. Angiography showed an occlusion of the whole length of the right superficial femoral artery without any abnormality of the aortoiliac or popliteal or lower leg vessels. The left superficial femoral artery was completely normal. A femoropopliteal bypass to the proximal popliteal artery with autologous saphenous vein was performed in 1974.

Histological examination of the artery showed an obstructive proliferation of the intima with recanalization and organized thrombus (*Figure 1*). The internal elastic membrane was interrupted and duplicated. The media showed disintegration of smooth muscle cells and elastin and elastin fibres, and reactive vessel proliferation. The external elastic membrane showed broad fibres scattering into the adventitial structures. There were no signs of atherosclerosis. This artery showed the characteristics of perimedial fibroplasia. During a 12 year follow-up there was no recurrence of symptoms or signs and the femoropopliteal bypass continued to function well.

Case 2. A 21-year-old man presented with a long history of intermittent claudication of the left leg and a short and disabling walking distance. He did not complain of rest pain. He did not smoke. On physical examination the femoral pulses were normal as were the pulsations over the right pedal arteries. There were no pulsations in the left popliteal or pedal arteries. Angiography showed an occlusion of the distal superficial femoral artery and of the popliteal artery, with a patent tibioperoneal trunk and a normal pattern of lower leg arteries. The abdominal aorta, the iliac arteries and the arteries of the right leg showed no abnormalities.

At operation in 1976 it was not possible to perform an endarterectomy or a bypass procedure because of hypoplastic saphenous veins. A lumbar sympathectomy was performed. After operation walking distance improved to 500 metres and the patient could fully resume his work as a house painter.

Because of progression of claudication a new angiogram was done 4 years later. There was total occlusion of the whole superficial femoral, the popliteal and the anterior tibial arteries. A femoropopliteal bypass to the distal popliteal artery using a human umbilical vein graft (Biograft®, Meadox Medicals, Oakland, New Jersey, USA) was performed.

Histological examination of the artery showed an abnormal configuration (*Figure 2*). There were not the usual and characteristic findings of atherosclerosis. The media was broad with a channel in the outer third. The elastin fibres were irregularly arranged and the media contained some collagen. The alcian blue stain demonstrated mucoid degeneration. The adventitia contained many elastin fibres. This lesion could be classified as medial dissection.

The postoperative course was complicated by occlusion of the bypass. Thrombectomy was unsuccessful. Two years later the patient developed rest pain and gangrene of two toes. Angiography showed an iliac obstruction. An iliofemoral bypass was performed. Six years after the first intervention, the left lower leg had to be amputated because of severe rest pain.

Case 3. A 36-year-old man presented with disabling intermittent claudication of the left leg, but without rest pain. Although he was a

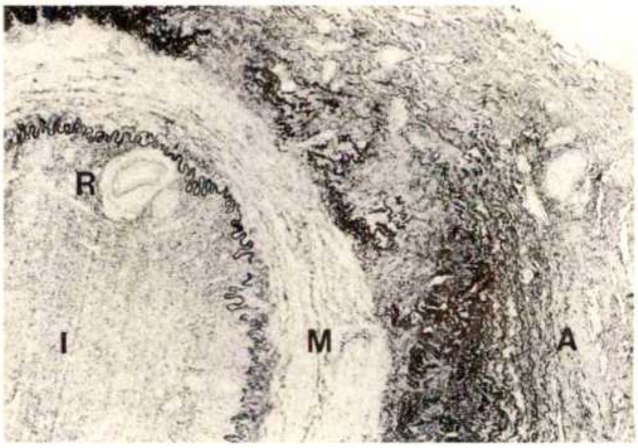

Figure 1 *Histology of perimedial fibroplasia of case 1. The lumen of the artery is occluded by an organized thrombus. The internal elastic membrane is focally interrupted and duplicated. The media shows degeneration of smooth muscle cells and elastic fibres. The main changes however are in the outer elastic membrane and adventitia with interruption of the former and loss of fibres in the latter (Verhoeff stain; original magnification × 56). I, intimal proliferation; M, media; A, adventitia; R, recanalization*

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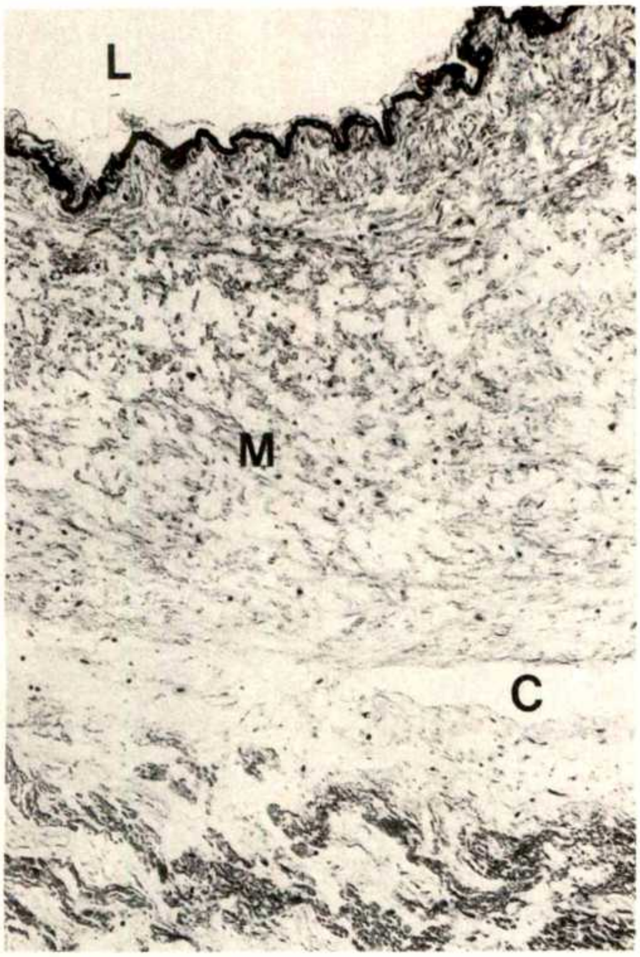

Figure 2 *Histology of medial dissection of case 2. The media is broad with irregular elastic fibres. In the outer zone of the media a channel is formed on the basis of mucoid degeneration (Verhoeff stain; original magnification × 140). L, lumen; M, media; C, channel*

cigarette smoker and occasionally complained of cold, pale fingers, there were no other signs of cardiovascular disease. On physical examination he showed normal pulsations over both femoral arteries and the right popliteal and pedal arteries. The left popliteal and pedal pulsations could not be felt. Non-invasive arterial testing of the lower extremities revealed a right ankle:brachial index of 1·35 and a left ankle:brachial index of 0·80. Angiography demonstrated an occlusion of the left popliteal artery, while the proximal and distal vessels were normal.

At operation in 1980 a part of the obstructed artery was resected. The artery was not adherent to the surrounding tissues. A bypass was performed using a human umbilical vein graft (Biograft).

Histological examination of the artery showed an accumulation of loose fibrous tissue in the intima, reduplication of the internal elastic lamina and some degenerated elastin fibres in the media (*Figure 3*). There was no atherosclerotic occlusive or inflammatory disease. These lesions could be classified as intimal fibroplasia. A 6 year follow-up of this patient was uneventful.

Abnormalities in the vasa vasorum were not seen in any of these patients and none had renal or other sites of fibrodysplasia identified by clinical or angiograpic investigation.

Discussion

Although atherosclerotic occlusive disease does occur in younger patients, it is rare enough to make a search for other causes of chronic ischaemia of a leg mandatory in this group of patients. Fibro(muscular) dysplasia is a non-atherosclerotic angiopathy that has remained an enigma since its original description in 1938[4]. Dysplastic arterial obstructions represent a heterogeneous group of lesions. Harrison and McCormack[5] tried to establish a uniform terminology for fibrous and fibromuscular non-atherosclerotic lesions. Their classification was based on the arterial layer – intimal, medial or adventitial – in which the lesions predominate. For a better understanding of the pathology of the specimens from our patients, the basic microscopic characteristics of the various lesions are given in *Table 1*. Division of fibrodysplasia into intimal fibroplasia, medial fibrodysplasia (four subgroups) and periarterial fibroplasia can be made.

Intimal fibroplasia is characterized by an accumulation of irregularly arranged subendothelial mesenchymal cells in loose, moderately cellular, fibrous tissue without lipid or inflammatory components. Reduplication of the internal elastic membrane is often seen, but the media and adventitia show little alteration.

In medial fibrodysplasia four subgroups can be defined. Medial fibroplasia, with mural aneurysm formation, is well known because of the 'string of beads' visible on angiography. This appearance is produced by local stenoses, due to thickened fibromuscular ridges, alternating with areas of mural thinning. The muscle cells and degenerating muscle fibres are partly replaced by fibroplasia with loose collagen. The muscle cells become plump in outline and somewhat disoriented in accumulations of ground substance. The internal elastic lamella is deficient in the aneurysmal wall and there may be an increase in longitudinally oriented smooth muscle cells in the adventitia.

The second subgroup is perimedial fibroplasia. Microscopically it is characterized by an intense fibroplasia in the outer half of the media, usually replacing the external elastic membrane. This may result in a severely stenosing irregular lesion.

The third subgroup is medial hyperplasia in which the

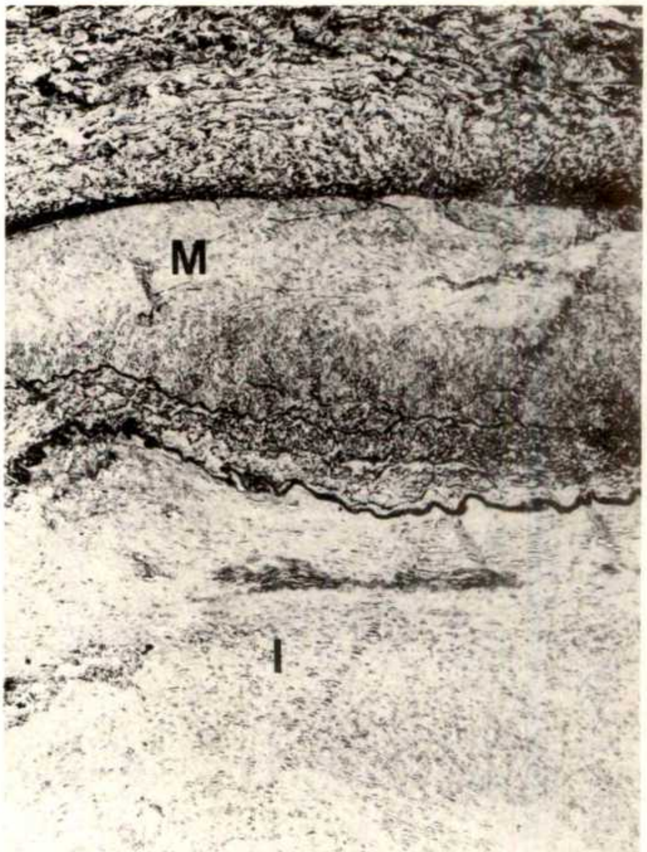

Figure 3 *Histology of intimal fibroplasia of case 3. There is intimal proliferation, reduplication of the internal elastic lamina and irregularity of elastic fibres in the media. (Verhoeff stain; original magnification × 35). I, intimal proliferation; M, media*

Table 1 *Major histopathological characteristics of the different types of fibrodysplasia*

Type	Intima	Internal elastic lamina	Media	External elastic lamina	Adventitia
Intimal fibroplasia	Accumulation of loose fibrous tissue	Often reduplication	Normal	Normal	Normal
Medial fibrodysplasia					
Medial fibroplasia	Normal	Deficient in aneurysms	Muscle cells and degenerated elastic fibres replaced by fibroplasia and loose collagen; muscle cells plump and disorientated	Normal	Sometimes increase of longitudinally oriented smooth muscle cells
Perimedial fibroplasia	Normal		Intense fibroplasia in outer half	Often replaced by fibroplasia	Normal
Medial hyperplasia	Normal	Normal	Hyperplasia of smooth muscle cells	Normal	Normal
Medial dissection	Sometimes secondary fibroplasia	Normal	Channel in outer third, zones of fibroplasia		Sometimes fibroplasia
Periarterial fibroplasia	Normal	Normal	Normal	Normal	Fibroplasia

obstruction is primarily produced by hyperplasia of smooth muscle cells without medial disruption and without an increase in ground substance. There is little alteration in intima, adventitia or elastic lamina.

The final subgroup of medial fibrodysplasia is medial dissection. A channel is located on the outer third of the media. The media, particularly around the new channel, displays zones of fibroplasia replacing the degenerating elastic fibrils. There may be slight adventitial fibroplasia.

The least common fibrodysplastic lesion is periarterial fibroplasia in which fibroplasia with collagen surrounds the adventitia and extends into the periarterial fatty tissue.

When this classification is applied to the patients in the present series, the lesions of case 1 can be best described as perimedial fibroplasia, the lesions of case 2 as medial dissection with secondary intimal fibroplasia and those of case 3 as intimal fibroplasia. There was otherwise no specific pattern to the site of the fibrodysplasia.

The only previous report of pathologically confirmed fibromuscular dysplasia of the femoropopliteal artery describes internal fibrous hyperplasia, disruption of the internal elastic lamella and intimal cushion formation[3]. This specimen should probably be classified as intimal fibroplasia. The present report of medial dissection and perimedial fibroplasia is the first description of a manifestation of these two types of fibrodysplasia involving the femoropopliteal arteries.

Although Tisnado *et al.*[2] describe a possible fibrodysplasia of the popliteal artery, diagnosed from its beaded appearance on angiogram, there was no histological confirmation.

Aetiological factors contributing to fibrodysplasia have been the subject of much speculation. The influence of hormones is likely since most of the patients described in the literature are female and it is known that certain smooth muscle cells and fibroblasts exposed to oestrogens exhibit increased synthesis of proteinaceous substances, including collagen[6]. Unusual physical stretching of the artery may also be associated with fibrodysplastic changes, and this stretching may increase the production of fibrous tissue. This theory is supported by the finding that clinical stretching of smooth muscle cells in tissue culture produces a marked increase in the synthesis of collagen and certain acid mucopolysaccharides[7]. The association between fibrodysplasia and diseases such as ankylosing spondylitis, scleroderma and Reiter's syndrome may suggest that an autoimmune process plays a part in the aetiology of some cases. Mural ischaemia by compromised vasa vasorum or popliteal artery entrapment may also contribute to the formation of dysplastic arteries. Experimental studies lend credence to this theory[8].

In the present series none of these contributing factors seem to apply. Since there were no angiographic signs of deviation of the popliteal arteries and no abnormal course of the arteries found at operation, we feel that entrapment is not an aetiological factor in the development of fibrodysplasia in these patients.

Regarding the specific angiographic appearances of fibrodysplasia the following remarks may be made. Fibrodysplastic disease has been described as having a localized 'string of beads' or tubular angiographic appearance, although the picture of intimal fibroplasia is that of a smooth, fairly focal, stenotic lesion. The typical and well known beaded appearance of medial fibroplasia results from aneurysmal dilatation of thinned areas of the arterial wall. The beads are wider than the uninvolved artery, a point which allows angiographic differentiation from perimedial fibroplasia in which small beads are visible. Medial hyperplasia shows a smooth linear stenosis. Dissection is also recognized as a radiological manifestation of this disorder[9]. These angiographic appearances are only visible at an early stage and could not be demonstrated in the patients described because they all had total occlusions. Although standard vascular surgical techniques, such as bypass procedures, are suitable for the treatment of fibrodysplastic disease of the femoropopliteal artery, percutaneous transluminal angioplasty may be applicable to the treatment of some lesions. This report demonstrates the need to consider fibrodysplasia, besides atherosclerosis, entrapment, cystic degeneration and trauma, as a possible cause of occlusive disease of the femoropopliteal arteries.

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Short note

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Operative cholangiography in elective cholecystectomy

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Since its introduction to biliary surgery by Mirizzi in 1932[1], cholangiography has gained in popularity. Its major contribution has been to decrease the number of negative common bile duct explorations while increasing the positive exploration rate[2], thus decreasing the overall morbidity and even mortality rates[3–8]. The arguments in favour of adopting routine cholangiography were to find clinically unsuspected common bile duct stones[9–11] and to obtain an anatomical road map of the extrahepatic bile duct system, thus preventing common bile duct injuries[12,13]. This led to the conclusion that operative cholangiography is indicated during all cholecystectomies[2,13].

We have analysed a series of elective cholecystectomies where cholangiography was used selectively by some surgeons or routinely by others in order to assess the value of routine radiography and the safety of a selective policy.

Patients and methods

In a 10-year period (1975–85) 1074 patients underwent elective cholecystectomy, of whom 323 were lost for follow-up. The remaining 751 patients were followed for a mean of 61 (range 27–124) months. Mean age was 57 (range 15–89) years; women outnumbered men in a ratio of 2:1. Patients with a history of or present jaundice, with a dilated common bile duct, palpable bile duct stone or positive radiological and/or sonographic results for stones in the bile duct were not included in this analysis as cholangiography was indicated in these patients. Patients suffering from liver or pancreatic disease were excluded as a main selection criterion for cholangiography was liver function tests, whose findings may be abnormal in this group of patients. The operation was performed either by five fully trained surgeons or by a number of residents under supervision.

Selective cholangiography was performed in 171 patients. The following indications for selective cholangiography were: (1) abnormal liver function tests (alkaline phosphatase (ALP), glutamate oxaloacetate transaminase (SGOT), bilirubin (BIL), lactic dehydrogenase (LDH); (2) small gallstones; (3) a solitary faceted gallstone. In addition, cholangiograms were performed in 228 operations where the findings did not fulfil the indications mentioned. Altogether, no cholangiogram was performed in 352 patients. The cholangiogram was performed with a Ranzi cannula inserted through the cystic duct, but in six cases this was not technically feasible; in these cases the cystic duct was presumed to be too small for stone passage and no cholangiogram was performed. A Siemens (Erlangen, FRG) C-arm image intensifier with an image retention facility was used for real time investigation and radiology. Radiographs were taken only in cases of unclear real time findings. Five to seven millilitres of contrast medium (Uromiro, Gerot Pharmazeutika, Vienna, Austria) diluted with 15 ml of saline was injected, and the progress of contrast medium monitored on the screen. Some patients, however, required more contrast medium for adequate assessment.

For this analysis, all patients underwent physical examinations and blood samples were taken for liver function tests. In those patients with abnormal liver function tests, ultrasonography or retrograde endoscopic cholangiography was carried out.

Results

Of 171 patients who had a cholangiogram performed according to the indications defined above, 56 (32·7 per cent) had a stone in the duct, whereas 112 (65·5 per cent) did not. In three (1·8 per cent) patients the cholangiogram gave a false positive result, prompting unnecessary choledochotomy. Routine cholangiography was performed in 228 patients and gave a correct negative result in 224 cases (98·2 per cent) and a false positive result in four examinations (1·8 per cent) as proven by choledochotomy and a repeat cholangiogram. All patients who were found to have common bile duct stones had abnormal liver function tests. Considering all patients with abnormal liver function tests, 22 per cent of those with one parameter elevated had stones, while the frequency of stones in patients with two or more abnormal tests ranged from 33 to 64 per cent (*Table 1*). On the other hand, of those with no duct stones only 15 per cent had an abnormal liver function test, mainly due to fatty liver change. *Table 2* depicts the accuracy of cholangiography and liver function tests. From these figures a predictive value of 100 per cent was calculated for a negative liver function test and negative cholangiography[14]. The predictive value for an abnormal liver function test was 33 per cent and

Table 1 *The frequency of common bile duct stones in relation to the number of abnormal liver function tests*

No. abnormal liver function tests	No. patients	No. patients with duct stones
1	92	20 (22)
2	42	17 (40)
3	22	14 (64)
4	15	5 (33)
Total	171	56 (33)

Values in parentheses are percentages

Table 2 *The accuracy of operative cholangiography and liver function testing in the prediction of common bile duct stones*

	No. patients	
Result	Operative cholangiography ($n = 399$)	Liver function test ($n = 751$)
Positive	56(14·0)	56(7·5)
Negative	336(84·2)	580(77·2)
False positive	7(1·8)	115(15·3)
False negative	0	0

Values in parentheses are percentages

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for positive cholangiograms 88 per cent. In all of the 399 patients having had a cholangiogram and those 352 not having had a cholangiogram no retained duct stones became evident.

Discussion

There is little doubt of the importance of operative cholangiography[2,3]. Recently a number of studies have been published on the role of routine cholangiography. Unsuspected duct stones have been found by routine cholangiography in 1·2–12·4 per cent (mean 6·2 per cent) of patients undergoing elective cholecystectomy[9–11]. On the other hand, large series of cholecystectomies without cholangiography have been reported with an incidence of residual duct stones of only 0·3 per cent[5,15]. The discrepancy between the percentage of duct stones detected by routine radiography and that of duct stones becoming symptomatic after surgery may be due to spontaneous passage of some stones through the papilla of Vater; many may remain asymptomatic[15]. It is debatable whether a 0·3 per cent incidence of residual duct stones can be tolerated by omitting cholangiography. It is our opinion that with the advent of safe endoscopic extraction of retained duct stones such a percentage is acceptable. Nevertheless, it was our intention to avoid any retained stones by carefully targeting cholangiography on the basis of abnormal liver function test and anatomical observations. The argument that duct injuries can be prevented by routine cholangiography is invalid since duct lesions are mainly a technical problem, as the majority of strictures occur after inappropriate clamping in the presence of bleeding. This can be avoided by good technique[16].

In contrast, 2–12 per cent of cholangiograms gave false positive results leading to unnecessary common bile duct exploration, thereby increasing the morbidity associated with elective cholecystectomy[4–8]. Our findings are in line with those of other authors[17], in so far as the entire liver chemistry profile (ALP, BIL, LDH, SGOT) seems to be a reliable indicator of duct stones. In our series there was not a single stone that was not associated with one or more abnormal liver function tests. The less reliable predictive value of positive liver function tests may derive from the fact that patients with unsuspected liver disease are included in this analysis.

Since liver function tests may vary by up to 10 per cent for enzyme determinations and by as much as 5 per cent for bilirubin determination, a false negative liver function test profile associated with a duct stone is a theoretical possibility. Therefore, small stones should be accepted as an indicator for cholangiography. From this experience we recommend performing cholangiography on a selective basis with the selection criteria described above. Selective cholangiography is safe, and cuts time and costs.

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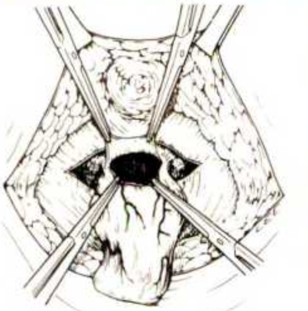

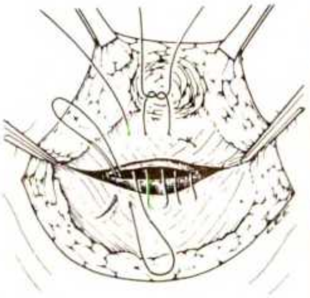

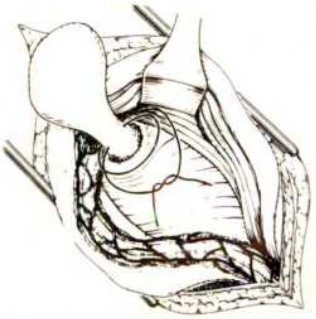

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Br. J. Surg. 1990, Vol. 77, April,
401–404

Effect of low dose recombinant interleukin 2 plus indomethacin on mortality after sepsis in a murine burn model

Under anaesthesia, 129 8-week-old male A/J mice were subjected to a 25 per cent scald or sham burn and then resuscitated. They were divided at random into two groups. Mice from the first group were allocated into two groups. Mice from the first group were allocated into four subgroups to receive 6 days intraperitoneal (I.P.) injections as follows: (i) recombinant human interleukin 2 (rhIL-2) (250 units day^{-1}); (ii) saline; (iii) indomethacin (5 μg^{-1} day^{-1}); or (iv) rhIL-2 (250 units) + indomethacin (5 μg). Sham burned mice served as no treatment controls. All animals were subjected to peritonitis induced by caecal ligation and puncture 10 days after the burn and mortality was assessed. Mice from the second group were allocated to two subgroups to receive 6 days intraperitoneal injections of: (i) rhIL-2 + indomethacin; or (ii) saline. Animals in this group did not undergo septic challenge. They were randomly killed on days 7, 9 or 10 after the burn. Their splenocytes were harvested and assayed for response to the mitogens phytohaemagglutinin (PHA) and concanavalin A (Con A), and for production of interleukin 2. Mortality rate in animals subjected to burn and septic challenge without treatment was 75 per cent; in mice receiving rhIL-2 alone it was 68 per cent, in mice receiving indomethacin alone it was 62 per cent (no significance) and in mice receiving rhIL-2 + indomethacin it was reduced to 38 per cent ($P<0{\cdot}02$). Splenocytes from animals receiving combination therapy had markedly improved responses to PHA on days 7 ($P=0{\cdot}01$), 9 ($P=0{\cdot}02$), and 10 ($P=0{\cdot}008$), and to Con A on days 7 ($P=0{\cdot}001$), 9 ($P=0{\cdot}002$) and 10 ($P=0{\cdot}001$), after burn injury. Interleukin 2 production was also significantly ($P=0{\cdot}004$) improved by therapy with rhIL-2 + indomethacin. These data suggest that low dose rhIL-2 in combination with indomethacin may have potential use in the therapy of burn victims.

Keywords: Interleukin 2, burns, therapy

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Death from sepsis with resultant multiorgan failure continues to be a major problem in dealing with patients following trauma. Baker *et al.* in 1980 reported that, of deaths occurring later than 7 days after injury, 78 per cent were due to sepsis[1]. In thermally injured patients 50–70 per cent of deaths are due to sepsis[2,3]. Donati *et al.* noted in 1983 that, if burn patients developed significant infection, the mortality rate rose to 80 per cent[4]. In separate reports Alexander *et al.*[5] and Casson *et al.*[6] studied the host defences in burn patients and found them to be compromised. Markley, in 1968, reported finding positive blood cultures in over half of thermally injured mice, most due to Gram-negative organisms[7]. Many authors have elucidated the specific immune defects after a burn, including defective neutrophil function[8], decreased lymphocyte blastogenesis in response to mitogens[9], changes in T cell subpopulations[10,11], and the presence of circulating immunosuppressive factors[12–15].

Impairment of interleukin 2 (IL-2) production has been demonstrated after a burn and is prolonged after T cell subpopulations have returned to normal[16]. It was therefore a logical step to attempt to restore immunocompetence after thermal injury by treatment with exogenous IL-2. We have previously reported the use of recombinant human interleukin 2 (rhIL-2) therapy in a murine burn sepsis model[17]. In these experiments, following a 25 per cent scald injury, rhIL-2 was injected by the intraperitoneal route for 6 days, and after 3 days of rest the animals were subjected to a septic challenge of peritonitis induced by a caecal ligation and puncture (CLP) procedure. The mortality rate was significantly reduced by IL-2 therapy. However, the dose used in this work, when adjusted for human therapy, is known to be associated with undesirable toxic side effects[18] and limits its usefulness for human application. The aim of this study was to assess the efficacy of a low dosage of rhIL-2 in treating burned animals which could, if effective, be used in human therapy.

Furthermore, it has also been shown by others that prostaglandin E$_2$ (PGE$_2$) inhibits IL-2 production by human cells[19]. We have shown that the cyclo-oxygenase pathway is probably involved in the mechanism of post-burn immunosuppression[20]. Therefore, we also assessed the use of the prostaglandin inhibitor indomethacin, alone and in combination with rhIL-2, as effective immunomodulators.

Materials and methods

Burn model

Male A/J mice, 7 weeks old, were obtained from Jackson Laboratories, Bar Harbor, Maine, USA. They were acclimatized for 1 week in the animal house under controlled conditions with water and mouse chow *ad libitum*. The mice were randomized into burn and sham burn groups, and were anaesthetized with pentobarbitone (1·25 mg mouse^{-1} in 0·25 ml saline) by intraperitoneal injection. The animals were shaved,

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over the dorsum and placed in a specially constructed mould exposing 25 per cent body surface area. Immersion of the mould in water at 90°C for 9 s resulted in a histologically proven full thickness burn. Resuscitation with 1 ml saline followed and the mice were caged in groups of five. Sham burn involved anaesthesia and shaving only. This protocol and all animal procedures were approved by the Standing Committee on Animals, Harvard Medical Area, under NIH guidelines.

Septic challenge

Under pentobarbitone anaesthesia the abdomens were shaved, opened, the caecum located and ligated at its base with 0/0 silk (Ethicon, Somerville, New Jersey, USA). The caecum was then punctured through and through with a 27 gauge needle and faeces expressed to ensure peritonitis. The abdomens were closed with 5/0 Ethilon® (Ethicon). Mortality was assessed at 96 h after CLP as this laboratory has consistently found maximum mortality occurs by this time using this model.

T cell mitogen responses

Splenocytes were suspended in RPMI 1640 medium with 2 mM l-glutamine, 5×10^{-5} M 2-mercaptoethanol, 1 per cent antibiotic antimycotic (penicillin 10 000 units, streptomycin 10 000 μg, amphotericin 2·5 μg ml^{-1}), gentamicin (40 μg ml^{-1}) and 10 mM HEPES (all reagents for cell washing and culture were obtained from Grand Island Biological Co., Grand Island, New York, USA). Cell suspensions were washed three times in this medium, centrifuging at 1500 r.p.m. for 10 min. Mononuclear cells were counted using Turk's solution and cultured in microtitre plates at 2×10^5 cells well^{-1} in 200 μl medium with 5 per cent heat-inactivated fetal calf serum (56°C, 30 min), with or without phytohaemagglutinin (PHA) at 5 μg ml^{-1} or concanavalin A (Con A) at 1·25 μg ml^{-1}. Assessment of cell viability was made using trypan blue and was always >95 per cent. The plates were incubated at 37°C in 5 per cent CO_2 for 24 h. At 24 h the plates were pulsed with 1 μCi well^{-1} of tritiated thymidine (^{3}HTdr) (New England Nuclear, Boston, Massachusetts, USA), and following a further 18 h of incubation the plates were frozen. Cells were harvested in a multi-automated sample harvester (Cambridge Technology, Cambridge, Massachusetts, USA). Incorporation of ^{3}HTdr was measured in a liquid scintillation counter (LKB Instruments, Gaithersburg, Maryland, USA).

Production and assay of interleukin 2

Splenocytes from individual mice were harvested, washed, counted as above, and adjusted to 2×10^6 cells ml^{-1}; 100 μl well^{-1} of these cells were placed on 96 well microtitre plates and incubated with Con A 1·25 μg ml^{-1} for 48 h. Supernatants were carefully withdrawn using a Pasteur pipette and frozen. For IL-2 assay the supernatants were thawed and diluted from 1:2 to 1:128 in the above medium with a 100 μl volume, and incubated for 1 h at 37°C in 5 per cent CO_2. CTLL-2 cells were washed free of T cell growth factor three times, diluted to 5×10^4 ml^{-1} and 100 μl added to each well. Cultures were incubated for 20 h, pulsed with ^{3}HTdr, harvested 4 h later and counted to assess uptake of ^{3}HTdr. A standard mouse IL-2 pool was given a value of 1 unit. IL-2 production was determined by comparison with this standard unit by probit analysis[21] with the aid of a computer program kindly provided by Dr Brian Davis. Suppression of IL-2 was calculated using the formula:

$$\% \text{ Suppression} = 100\left(1 - \frac{\text{mean IL-2 production in units for each individual mouse}}{\text{mean IL-2 production in units for the control group}}\right)$$

Treatment protocol

One hundred and twenty-nine mice were subjected to either a burn (112 mice) or sham burn injury (17 mice). They were randomly allocated to one of two major experimental groups. The first group was used to investigate the effects of various immunomodulating therapies on the mortalities after scald injury and subsequent septic challenge. This group consisted of 64 burned and 8 sham burned mice. The burned mice were further allocated to one of four treatment groups of 16 mice each. Treatment groups received by daily i.p. injection (beginning 1 day after burn injury) either: (i) 250 units rhIL-2 + 5 μg indomethacin mouse^{-1} (Merck and Co., West Point, Pennsylvania, USA), (ii) saline, (iii) 5 μg indomethacin, or (iv) 250 units rhIL-2. After 6 days of therapy the mice were allowed to rest for 3 days, then subjected to septic challenge by CLP as above. Sham burned mice received no therapy but were subjected to CLP.

The second experimental group was used to determine if the effects on mortality noted in the first part of the experiment were reflected by changes in the responses to the mitogens PHA and Con A, and in the production of IL-2. This group consisted of 48 burned mice allocated to one of two equal-sized treatment groups. One group received 250 units rhIL-2 + 5 μg indomethacin mouse^{-1} day^{-1}. The second group received intraperitoneal injections of saline. All mice were treated for 6 days. All injections were 1 ml in volume. Eight mice from each group were killed in a CO_2 chamber on days 7, 9, and 10 post-burn, their splenocytes harvested and mitogen responses assessed. Nine sham burned mice were untreated.

Statistical analysis

Statistical analysis was made using Student's *t* test for PHA, Con A, and IL-2 data and Fisher's exact test for survival data, using the computer program Tadpole (Biosoft, Milltown, New Jersey, USA). Significance was assumed at the 95 per cent confidence level.

Results

Survival after burn and sepsis

Sham burned animals had no mortality after sham burn and a 20 per cent mortality rate when subjected to CLP. In animals receiving a 25 per cent body surface area burn and subjected to CLP 10 days later, the mortality rate was 75 per cent. Therapy with low dose rhIL-2 alone (250 units) reduced the mortality rate slightly to 68 per cent (not significant). Similarly, treatment with indomethacin alone further reduced the mortality rate to 62 per cent, but again not reaching significance. However the combination of rhIL-2 plus indomethacin resulted in a significant reduction of mortality rate to 38 per cent ($P < 0·02$).

Restoration of in vitro *mitogen responses after* in vivo *therapy*

When the mitogen responses after burn and after therapy were studied, it was found that there was significant improvement in the responses of splenocytes from the rhIL-2 + indomethacin-treated mice to PHA on days 7 ($P = 0·01$), 9 ($P = 0·02$) and 10 ($P = 0·008$) post-burn compared with saline-treated animals (*Figure 1a*). The greatest enhancement (100 per cent) of PHA response was found on day 10 (*Figure 1b*).

There were similar improvements in responses to Con A after therapy with rhIL-2 + indomethacin on days 7 ($P = 0·001$), 9 ($P = 0·002$) and 10 ($P = 0·001$) (*Figure 2a*). The greatest enhancement of Con A response was found on day 7 post-burn (>100 per cent) (*Figure 2b*). In sham burned mice, overall responses to mitogens were surprisingly not significantly different from saline-treated burned animals, although in many individual measurements burned mice were indeed immunosuppressed.

The production of IL-2 post-burn and therapy was also examined, and it was found that on day 7 post-burn, saline-treated mice showed significantly suppressed IL-2 production ($P = 0·0001$) compared with sham burned animals (*Figure 3*). Furthermore, therapy of burned mice with low dose rhIL-2 + indomethacin resulted in a significant increase in IL-2 production ($P = 0·004$) compared with saline-treated burned mice.

Discussion

The results reported here demonstrate that the combination therapy of low dose rhIL-2 with indomethacin is able to improve cell-mediated immunity in burned mice, measured *in vitro*, and is associated with a significantly improved survival rate in burned mice subjected to septic challenge by CLP.

Many authors have attempted to abrogate the immunosuppression observed in thermally injured animals with a variety of immunomodulators including: vitamin A[22], *Corynebacterium parvum*[23], polymyxin B[24] and cyclophosphamide[25]. Zapata-Sirvent *et al.* reported improved survival rates with specific pharmacological therapy in burned mice in dosage regimens shown to improve cell-mediated immunity, when the animals were subjected to subsequent infectious challenge[25]. These drugs included cimetidine, cyclophosphamide, ibuprofen and cerium nitrate. It should be noted, however, that there were no controls used in the experiments for either vehicle or fluid volume, which in themselves are likely to affect survival after burning.

Hansbrough *et al.*[26] showed improvement in post-burn

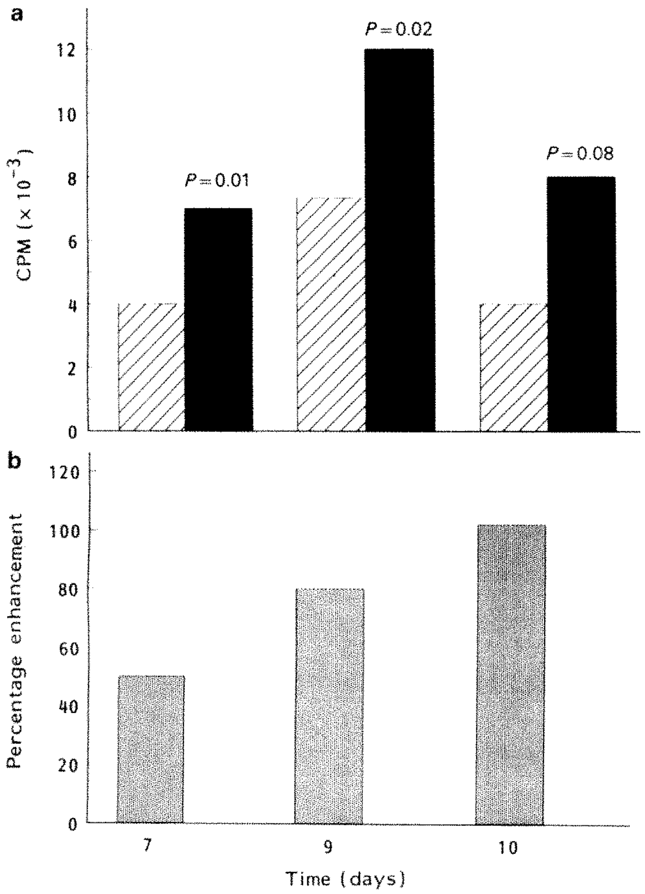

Figure 1 **a** *Responses to phytohaemagglutinin (PHA) by splenocytes from burned mice treated with saline (▨) or interleukin 2 + indomethacin (■). P values expressed as compared with saline-treated mice (n = 8 for each group on each day).* **b** *Percentage enhancement of responses to PHA post-therapy with interleukin 2 + indomethacin*

cell-mediated immunity using the prostaglandin inhibitors ibuprofen and indomethacin, but this animal model did not include an infectious challenge. Waymack *et al.*[23] in their burn model included a single injection of bacteria into the peritoneal cavity and reported improved survival rates after administration of pharmacological agents, including *C. parvum* and TP-5. However, a single dose of bacteria does not resemble the continuous infectious challenge that occurs in thermally injured patients, which is probably more nearly duplicated by the CLP model used in the present study.

Over recent years the role of prostaglandins in the regulation of the immune response has been studied. They have been shown to be immunosuppressive probably by activation of suppressor cells[27,28]. The release of large amounts of prostaglandins of the E series as a direct consequence of traumatic and burn injuries is well documented[29]. Many authors have reported on the immunomodulating effects with prostaglandin synthetase inhibitors. Indomethacin has been shown to reverse depressed cellular immunity seen with Hodgkin's disease[30], and it corrected immunosuppression and slowed tumour growth in mice with chemical and virus-induced tumours[31]. Webb and Jamieson described a mouse spleen cell which suppressed the PHA and Con A response of normal mouse spleen cells; this suppression was blocked by indomethacin and stimulated by PGE$_2$[32]. It has been shown that post-burn immunosuppression seen in a mouse model could be abrogated by removal of burn eschar or infusion of peritoneal macrophages from unburned mice. The authors went on to suggest that it was the presence of prostaglandin-producing macrophages that led to the observed immunosuppression[33].

Miller *et al.* suggested that the presence of prostaglandin-producing macrophages is a normal response in a local wound, and that it is the quantity of these inhibitory-suppressor macrophages that is the important factor in host defence[34]. The implication is that thermal trauma results in local immunosuppression, and with sufficient injury spills over and initiates harmful systemic effects constituting systemic immunosuppression[34]. One of the major inhibitors of IL-2 production in human cells is PGE$_2$. PGE$_2$, a product of the cyclo-oxygenase pathway, is increased in burn patients, and circulating lymphocytes in these patients have been shown to be more sensitive to its effects than those from normal individuals[35,36].

IL-2 induces T cell proliferation, induces IL-2 receptors, enhances production of T cell growth factor and γ-interferon, and induces T cells to become cytotoxic[37]. In large doses (> 90 000 units kg^{-1} day^{-1}) IL-2 causes significant side effects, e.g. fever, chills, nausea, vomiting, tachycardia and general

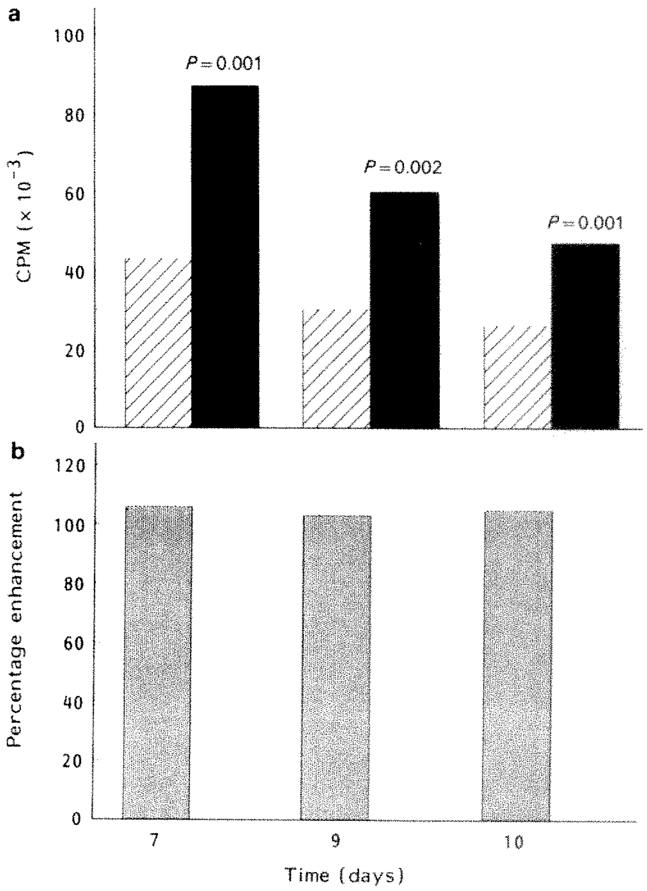

Figure 2 **a** *Responses to concanavalin A (Con A) by splenocytes from burned mice treated with saline (▨) or interleukin 2 + indomethacin (■). P values expressed as compared with saline-treated mice (n = 8 for each group on each day).* **b** *Percentage enhancement to responses to Con A post-therapy with interleukin 2 + indomethacin*

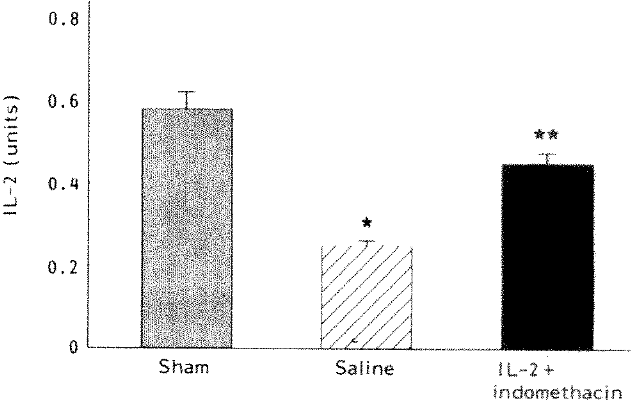

Figure 3 *Production of interleukin 2 by splenocytes from sham burned mice (▩), burned mice treated with saline (▨) or interleukin 2 + indomethacin (■). *P = 0·001 compared with sham burned mice; **P = 0·004 compared with saline-treated mice*

malaise[37]. We have previously shown in the same burn sepsis model that rhIL-2 (16000 units day^{-1}) improves survival compared with untreated animals[17]. A dose of 250 units day^{-1} also showed beneficial effects on survival but this benefit did not reach significance. Gough *et al.*[17] showed that mouse spleen cells were more responsive to mitogen stimulation with PHA and Con A when IL-2 was added *in vitro*, and went on to suggest that IL-2 had improved T cell function by increasing IL-2 receptor expression. This group also noted that endogenous IL-2 production was suppressed by *in vitro* IL-2 therapy when compared with controls. However, the data presented in this report indicate that endogenous production of IL-2 is increased after therapy with low dose rhIL-2 in combination with indomethacin, possibly accounting for the increased mitogen responses and improved survival rates seen in the present experiments. The dose of rhIL-2 used in this report (i.e. 250 units day^{-1} or 10000 units kg^{-1} day^{-1}), when adjusted for human therapy, is less than the doses used *in vivo* by investigators such as Rosenberg *et al.*[38] in cancer therapy. Furthermore, the dose of indomethacin when converted to man units by weight would be equivalent to 14 mg day^{-1}, a very low dose and likely to be without toxicity even in thermally injured patients.

We feel that this therapy may have clinical therapeutic usefulness in reducing mortality after sepsis in thermally injured patients.

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Intermittent hepatic dearterialization induces glucose intolerance: an experimental study in the rat

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Intermittent hepatic dearterialization is used in the palliative treatment of liver malignancy. However, its metabolic consequences are not established. Therefore the influences of the procedure on the plasma insulin, glucagon and glucose responses were studied in healthy rats and in rats with a tumour inoculated subcapsularly into the liver. To study the influence on stimulated islet hormone secretion we infused arginine intravenously (7 mg/min) for 30 min, because arginine is known to stimulate the secretion of both insulin and glucagon. During hepatic dearterialization, hyperglycaemia developed; mean(s.e.m.) blood glucose levels after 60 min of dearterialization were 20·2(1·3) mM *versus 14·7(1·5)* mM *in controls* ($P<0{\cdot}001$)*. Concomitantly, compensatory hyperinsulinaemia and hypoglucagonaemia occurred. Furthermore, during both dearterialization and in the immediate reperfusion phase, the arginine-induced increase in plasma insulin levels was impaired* ($P<0{\cdot}001$)*, whereas the arginine-induced increase in plasma glucagon levels was not significantly affected. These changes were qualitatively the same in tumour-free and tumour-bearing rats. We conclude that glucose intolerance develops during selective hepatic dearterialization, which is evident both from basal hyperglycaemia and impaired insulin secretion.*

Keywords: Hepatic dearterialization, liver cancer, glucose intolerance, insulin secretion, glucagon secretion, *in vivo*, rat, arginine

Intermittent hepatic dearterialization is sometimes undertaken in the palliative treatment of liver malignancy[1–4]. The development of this mode of treatment has been stimulated by the possibility of using implantable occluders and repeating the ischaemic treatment frequently over long periods[5]. The metabolic consequences of intermittent hepatic dearterialization are, however, not established. The fact that the liver plays a central role in glucose metabolism makes it possible that repeated periods of hepatic ischaemia affect the glucose homoeostatic mechanisms. In fact, a previous study has shown that, in the reperfusion phase after a 60 min dearterialization in the tumour-bearing rat, the plasma insulin response to glucose infusion is inhibited[6]. However, the influences during the dearterialization itself are not known and therefore, in an experimental model in the rat, we have now examined the possible influences of both hepatic dearterialization and reperfusion on plasma levels of glucose, insulin and glucagon, in both tumour-free and tumour-bearing rats. We infused arginine intravenously during the dearterialization as well as in the immediate reperfusion phase. Arginine is known to stimulate both insulin and glucagon secretion[7] and to stimulate insulin secretion by a mechanism that is different from that of glucose[8]. Hence, the design of this study allowed us (1) to investigate the effects of hepatic dearterialization and reperfusion on both insulin and glucagon secretion and (2) to determine whether the inhibition of insulin secretion, described previously, after hepatic dearterialization[6] is specific for glucose or is seen also for a secretagogue with another mechanism of action.

Materials and methods

Animals

Male inbred Wistar–Furth rats (ALAB Laboratory, Solna, Sweden), weighing 250–350 g, were used. They were kept on a standard laboratory diet (Astra-Ewos, Södertälje, Sweden) with tap water *ad libitum*.

Anaesthesia

The laparatomies for tumour cell inoculation, the dearterialization procedure and the arginine infusions were all performed during anaesthesia induced by intraperitoneal injection of chloral hydrate (0·25 g/kg; Apoteksbolaget, Stockholm, Sweden).

Dearterialization procedure

In the anaesthesized rats, the falciform ligament, peritoneal attachments and gastroduodenal artery were divided. Then intermittent hepatic dearterialization was achieved by placing a vascular occluder on the proper hepatic artery for 1 h. Previous angiographic study has shown this technique of inducing hepatic ischaemia to be reversible[9]. Control rats underwent a sham operation, where all the divisions as above were performed but the vascular occluder was not applied.

Tumour inoculation

Tumour tissue was obtained from an N-methyl-N-nitrosoguanidine-induced adenocarcinoma of the rat colon, as previously described[10]. The tumour had undergone weekly intraperitoneal propagation for at least 40 generations before the start of the experiments. Tumour cell suspensions were prepared using a trypsin solution (0·25 per cent), and vital counts were made in a haemocytometer after adding trypan blue. In each rat, a 0·1 ml suspension of 1×10^6 viable cells was injected subcapsularly into the left lateral lobe of the liver via a small midline laparotomy. After 6–8 days the tumour had reached an approximate size of 0·3 cm^3, and the rats were then used for experimentation. This small tumour size did not affect the total liver volume. Also, the body-weight at the time of experiment did not differ between tumour-bearing and tumour-free animals.

Arginine infusion

During anaesthesia, a femoral artery and vein were cannulated with Portex® tubing (Hythe, Kent, UK). The venous cannula was connected to an infusion pump and used for the infusion of arginine (Sigma Chemical Company, St. Louis, USA) at 7 mg/min at a rate of 0·1 ml/min for 30 min. Blood samples were drawn from the arterial cannula into heparinized tubes before, during and after the arginine infusion. The

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samples were immediately centrifuged, and plasma was separated and stored at −20°C.

Experimental protocols

Arginine was infused into non-fasted healthy control rats and into tumour-bearing rats either during hepatic dearterialization or in the reperfusion phase immediately after the end of a 60 min dearterialization. Each rat underwent only one infusion. When infusing arginine during dearterialization, the infusion was started simultaneously with the application of occlusion. When infusing arginine during the reperfusion phase, the infusion was started 5 min after withdrawal of the occlusion. The groups and the numbers of animals in each group are shown in *Table 1*. Saline-infused controls were not included in this study because it has been shown previously that intravenous infusion of saline for 30 min does not affect plasma levels of glucose, insulin or glucagon[7].

Analysis

Plasma levels of insulin were determined with a radioimmunoassay[11] using guinea pig antiporcine insulin antiserum (Milab, Malmö, Sweden). ^{125}I-labelled porcine insulin and, as standard, porcine insulin (Novo Res Lab, Bagsvaerd, Denmark). Plasma glucagon levels were determined with a radioimmunoassay[12,13] using guinea pig antiporcine antiserum specific for pancreatic glucagon and ^{125}I-labelled porcine glucagon (Milab) and, as standard, porcine glucagon (Novo Res Lab). Plasma glucose levels were determined by the glucose oxidase method[14].

Statistics

Results are expressed as mean(s.e.m.). Two-tailed analysis of variance (ANOVA) and Student's t test were used for statistical evaluation.

Results

Effects of dearterialization on plasma levels of glucose, insulin and glucagon

The 60 min hepatic dearterialization induced hyperglycaemia, hyperinsulinaemia and hypoglucagonaemia (*Table 2*).

Arginine infusion in tumour-free rats

Arginine infusion promptly increased plasma levels of insulin ($P<0·001$) and glucagon ($P<0·001$) in the tumour-free control rats without dearterialization (*Figure 1*). During hepatic dearterialization, the arginine-induced increase in plasma insulin levels was impaired when compared with these controls ($P<0·01$). In contrast, the arginine-induced increase in plasma glucagon levels was not significantly affected by dearterialization. In the reperfusion phase, i.e. immediately after the end of the dearterialization, the plasma insulin response to arginine was, again, markedly impaired compared with the controls ($P<0·001$). The increase in plasma glucagon levels, i.e. the elevation above baseline levels, during arginine infusion in the reperfusion phase was not significantly different from that seen without a preceeding dearterialization (at 30 min the mean(s.e.m.) was +63(24) pg/ml and +131(33) pg/ml respectively).

Table 1 *Experimental groups and numbers of animals used in the study*

30 min arginine infusion	No. of rats	
	Tumour-free	Tumour-bearing
Alone	6	7
During 60 min hepatic dearterialization	7	7
In the immediate hepatic reperfusion phase	7	7

Table 2 *Plasma levels of glucose, insulin and glucagon in tumour-free and tumour-bearing rats, in controls without dearterialization and after 60 min of hepatic dearterialization*

	Tumour-free rats		Tumour-bearing rats	
	Controls	Dearterialization	Controls	Dearterialization
Glucose (mM)	14·7 (1·5)	20·2 (1·3)‡	15·0 (0·4)	21·2 (1·0)†
Insulin (microunits/ml)	24 (3)	39 (3)*	30 (3)	38 (5)*
Glucagon (pg/ml)	299 (22)	147 (40)‡	285 (20)	207 (39)*

Values are mean(s.e.m.) in samples taken before the arginine infusion in controls and after 60 min of hepatic dearterialization in the groups undergoing arginine infusion in the reperfusion phase. Probability level of random difference between the groups: * $P<0·05$; † $P<0·01$; ‡ $P<0·001$

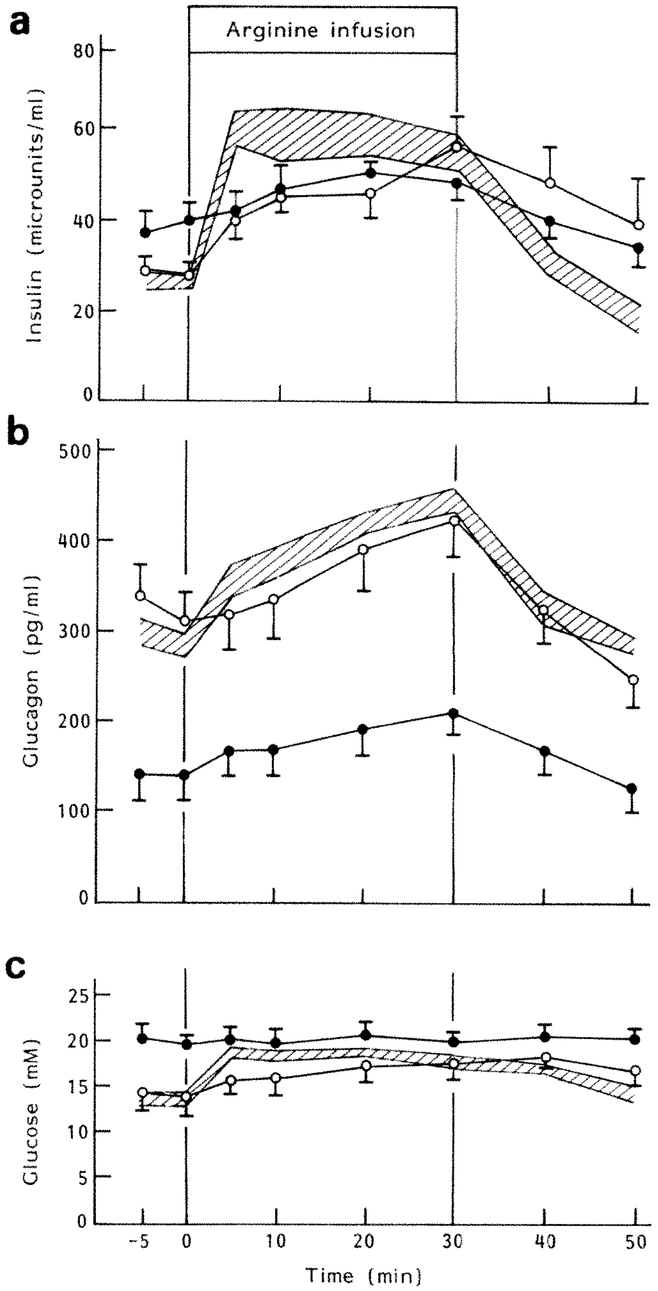

Figure 1 *Plasma levels of* **a** *insulin,* **b** *glucagon and* **c** *glucose before, during and after intravenous infusion of arginine at 7 mg/min for 30 min in groups of 6–7 rats. Values are mean(s.e.m.).* ○, *healthy tumour-free rats during hepatic dearterialization; or* ●, *in the immediate reperfusion phase after a 60 min preceeding dearterialization;* ▨, *controls without dearterialization*

Arginine infusion in tumour-bearing rats

Arginine infusion also increased plasma levels of insulin and glucagon in the tumour-bearing control rats without dearterialization (*Figure 2*). During dearterialization in the tumour-bearing rats, an impaired increase in plasma insulin levels was observed when compared with the controls without dearterialization ($P<0·05$), whereas the increase in plasma glucagon levels during

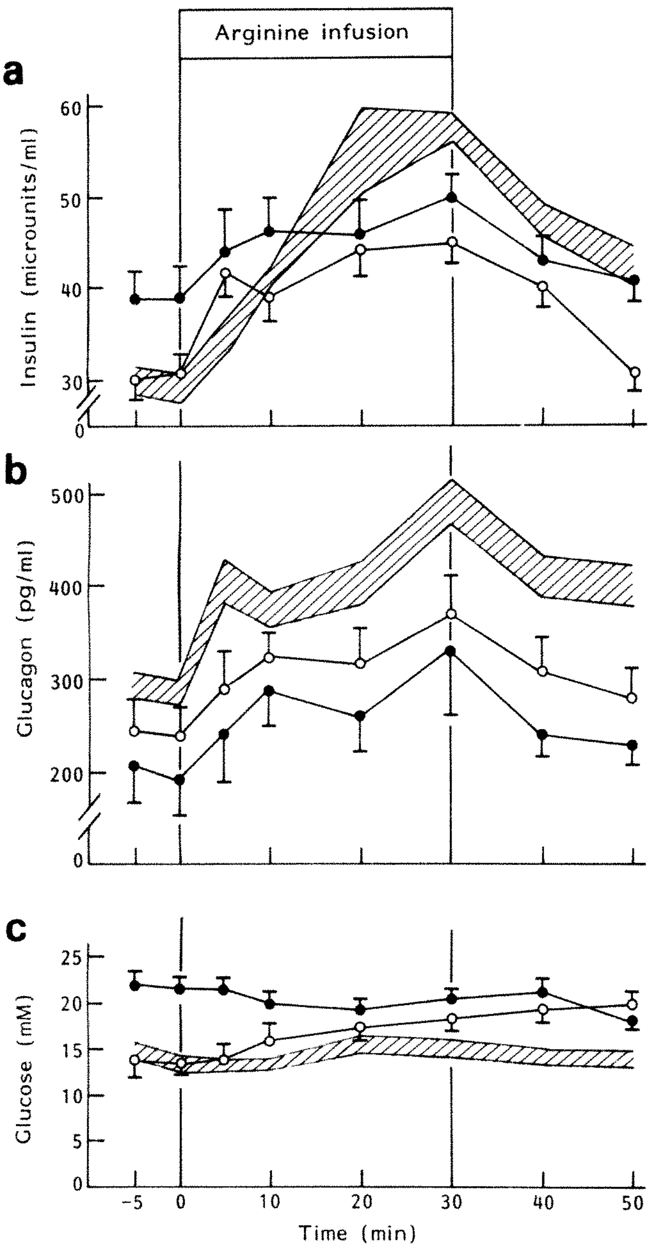

Figure 2 *Plasma levels of* **a** *insulin,* **b** *glucagon and* **c** *glucose before, during and after intravenous infusion of arginine at 7 mg/min for 30 min in groups of 7 rats. Values are mean(s.e.m.).* ○, *tumour-bearing rats during hepatic dearterialization; or* ●, *in the immediate reperfusion phase after a 60 min preceeding dearterialization;* ▨, *controls without dearterialization*

arginine infusion was not significantly different from controls. Also, in the reperfusion phase, the increase in plasma insulin levels during arginine infusion was markedly impaired ($P<0{\cdot}001$). However, the arginine-induced increase in plasma glucagon levels, i.e. the elevation above baseline, in the reperfusion phase was not significantly different from that in the controls (at 30 min the mean(s.e.m.) was +114(27) pg/ml and +155(24) pg/ml respectively).

Discussion

Previous studies have shown that in the reperfusion phase after a 60 min hepatic dearterialization in the tumour-bearing rat, the plasma insulin response to glucose infusion is inhibited[6]. We studied in more detail the metabolic consequences of hepatic dearterialization using a recently developed experimental model in the rat, in which intermittent selective hepatic dearterialization is possible[6]. The effects of the hepatic dearterialization on the plasma levels of glucose, insulin and glucagon, both in the basal state and after intravenous infusion of arginine, were studied. Furthermore, the effects during both hepatic dearterialization and in the immediate reperfusion phase were studied in both healthy, control rats and rats with a tumour inoculated into the liver. Arginine was infused because: (1) arginine stimulates glucagon secretion as well as insulin secretion[7], and (2) arginine stimulates insulin secretion by cellular mechanisms different from those of glucose[8].

Responses to intermittent hepatic dearterialization-induced hyperglycaemia, hyperinsulinaemia and hypoglucagonaemia were the same in tumour bearing rats as in controls. This shows that the observed effects are caused by the dearterialization procedure only and not by the existence of the tumour. After 60 min of hepatic dearterialization, though hyperinsulinaemia occurred, hyperglycaemia had developed. This indicates that the procedure induces glucose intolerance. This is probably due to reduced peripheral insulin sensitivity concomitant with unaffected glucose delivery from the liver, since it was shown previously that the elimination of infused ^{3}H-glucose was inhibited in hepatically dearterialized rats whereas the hepatic release of glucose was unaffected[15]. Probably as consequences of this hyperglycaemia, both hyperinsulinaemia and hypoglucagonaemia developed. The mechanism behind the reduced peripheral glucose uptake is not known, but may possibly be explained by the effect of metabolites released from the liver during dearterialization.

The arginine-induced increase in plasma insulin levels was impaired by the dearterialization. This impairment persisted into the reperfusion phase. This effect is most likely to be secondary to impairment of the insulin secretion but could theoretically also be due to exaggerated liver extraction of insulin. However, since hyperinsulinaemia developed in the basal, non-stimulated condition but an impaired increase in plasma insulin occurred during arginine infusion, it is unlikely that the dearterialization affects the hepatic extraction of insulin; if so, changes in plasma insulin levels in the same direction would have been expected under basal and stimulated conditions. Also, liver failure, which resembles some characteristics of dearterialized liver, is accompanied by impaired liver extraction of insulin, which leads to hyperinsulinaemia[16,17] and not to impaired increases in plasma insulin levels as we observed during arginine infusion. A possible explanation for the inhibited insulin secretion could be activation of the sympathetic nerves during the dearterialization, because such activation is known to inhibit insulin secretion[18]. Another possibility could be the release of metabolites from the liver that inhibit insulin secretion. Taken together with the previous result of inhibited glucose-stimulated insulin secretion after hepatic dearterialization[6] it could, however, be concluded that the inhibition of insulin secretion is potent and mediated through mechanisms shared by glucose and arginine[8].

In conclusion, our study shows that glucose intolerance develops during selective intermittent hepatic dearterialization in this experimental model in the rat, as evident both from hyperglycaemia and impaired insulin secretion. In contrast, the increase in plasma glucagon levels during arginine infusion was not affected by hepatic dearterialization, either during the dearterialization procedure or in the reperfusion phase. Hence, arginine-induced glucagon secretion, in contrast to insulin secretion, seems unaffected by hepatic dearterialization.

Acknowledgements

The authors are greatful to Lena Kvist and Adriana Ferreira for technical assistance. The study was supported by the Swedish Medical Research Council (grants nos. 14X-6834 and 17X-7183) and by the Faculty of Medicine, Lund University.

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Epidermal growth factor increases tensile strength in intestinal wounds in pigs

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Growth factors enhance tensile strength, angiogenesis and collagen synthesis in skin wounds. The effects were studied of a continuous intraperitoneal infusion of epidermal growth factor (EGF) on the mechanical properties of healing in linear full-thickness wounds of the stomach, ileum and colon of young pigs ($n = 16$, *mean(s.d.) body-weight 20·1(1·9) kg). In half the animals an osmotic minipump was implanted into the peritoneal cavity to deliver recombinant human EGF at a rate of 0·5 µg kg*$^{-1}$ *24 h*$^{-1}$. *Animals were killed at 5 days and the integrity of a 20-mm ring of intestine was tested for tensile strength. Breaking strength (g mm*$^{-2}$*) of the intestinal wounds in untreated pigs* ($n = 8$) *was: stomach 28·0(2·0), ileum 46·8(4·8), colon 85·6(4·2). Intestinal wounds in pigs* ($n = 8$) *receiving supplemental EGF had significantly increased breaking strength: stomach 32·4(2·2)* ($P < 0{\cdot}05$), *ileum 56·8(5·4)* ($P < 0{\cdot}05$), *colon 96·0(3·8)* ($P < 0{\cdot}01$) *compared with untreated animals. At 5 days after the initial injury intraperitoneal EGF increases the tensile strength of intestinal wounds in pigs.*

Keywords: Epidermal growth factor, wound, experimental, intestinal

The aim of the study was to discover whether epidermal growth factor (EGF) has a stimulatory effect on intestinal wound healing similar to its effect on skin wound healing[1–3]. Several investigators have established the key role of growth factors in regulating the recruitment of leucocytes, monocytes and fibroblasts into a wound area[4]. In this situation growth factors function as chemoattractants. The most important element of intestinal or anastomotic wound healing occurs in the submucosa where collagen is synthesized and increased tensile strength is derived[5]. EGF not only attracts fibroblasts into wounds but also increases fibroblast mitogenesis, production of collagen, angiogenesis and synthesis of non-collagenous protein such as fibronectins and hyaluronic acid[4,6,7]. Investigation of the effects of EGF on intestinal wound healing is particularly relevant because EGF is synthesized and secreted from the upper gastrointestinal tract in saliva and duodenal juices[8–10]. Supplemental EGF could be incorporated into biomaterials utilized at intestinal anastomoses to enhance healing in clinical situations where wound failure is a potential hazard.

Materials and methods

Sixteen weanling pigs of Cotswold breed weighing 18–22 kg and aged between 6 and 7 weeks at the time of operation were used for the experiments. Male and female pigs were randomly allocated to both treatment groups. For 12 h before operation the pigs were fasted but allowed free access to water. Anaesthesia was induced with pentobarbital and maintained with endotracheal intubation and artificial ventilation with nitrous oxide and oxygen. Triplopen® (Glaxo Laboratories Ltd., Greenford, UK) antibiotic was administered after induction of anaesthesia, and intramuscular analgesia was administered at 12 and 24 h after operation. All operations were performed by one surgeon. Male or female pigs from the same litter were operated on in pairs and one from each pair was randomly allocated to receive EGF treatment ($n = 8$) or no treatment ($n = 8$).

Standardized full-thickness linear incisions were made in the anterior wall of the antrum of the stomach, the antimesenteric border of the ileum, and the caecum. The intestinal wounds were identically sited in all pigs: in the stomach beginning 1 cm from the pylorus and extending proximally; in the ileum beginning 1 cm from the ileocaecal valve and extending proximally; and in the caecum beginning 5 cm from the caecal pole and extending distally.

Stomach wall was too thick to be closed with a stapling instrument and therefore all gastric wounds were closed with interrupted extramucosal sutures of 3–0 Vicryl® (Ethicon Ltd., Edinburgh, UK). Ileal and colonic wounds were closed with a linear 55-mm TA-55 stapling instrument (US Surgical Corporation, Ascot, UK) or interrupted extramucosal sutures of 3–0 Vicryl®. In half the pigs an osmotic minipump of 4 ml capacity (Alza Corporation, Palo Alto, California, USA) was implanted into the peritoneal cavity to deliver human recombinant EGF dissolved in normal saline at a rate of 0·5 µg kg^{-1} 24 h^{-1}. Access to water was allowed after recovery from anaesthesia and normal feeding was resumed 24 h after operation. Pigs were killed in pairs at 5 days; the viscera were excised, placed immediately in saline at 4°C and removed to the laboratory for tensile mechanical tests. A cutting instrument consisting of two scalpel blades mounted in parallel 20 mm apart was used to remove a ring of bowel wall oriented so that the intestinal wound was at 90° to the cut. A tensiometer (JJ Instruments, Model No. M5K) with a fixed lower clamp and a movable cross-head was used for tensile testing. After removal of sutures or staples this ring of bowel wall was mounted on L-shaped hooks passed through the lumen in order to avoid the need to grip the intestinal wall (*Figure 1*). The rate of extension (equivalent to the cross-head speed of the machine) of the intestinal rings was 50 mm min^{-1} for all experiments, and chart speed while testing was 50 mm min^{-1}.

Maximum tensile strength (breaking strength) was calculated by dividing the load required to rupture the anastomosis (F_{max}) by the cross-sectional area. Width was multiplied by thickness to derive cross-sectional area of the intestinal ring. Thickness was calculated by placing a strip of intestine between glass slides and measuring the composite thickness without compression, then subtracting thickness of the glass slides to derive intestinal wall thickness. A load–extension curve was produced for each specimen (*Figure 2*) which enabled calculation of: (i) breaking strength (F_{max} expressed in g mm^{-2}); (ii) maximum tensile strain (expressed as the percentage by which the specimen elongates before rupture as a proportion of its initial length); and (iii) modulus of elasticity (related to tan θ, the ratio of stress to extension when the specimen undergoes linear elastic deformation).

Specimens from ten pigs (five from each treatment group) were fixed in 10 per cent formol saline for histological examination. Paraffin sections were cut at 3 µm and stained by the haematoxylin–eosin and van Gieson methods. Collagen deposition was assessed by light microscopy. Statistical analysis was by Student's t test for paired data.

Results

Mean(s.d.) body-weight of the pigs was 20·1(1·9) kg. Weight did not change during the 5-day experimental period. There

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were no instances of intestinal wound failure, peritoneal sepsis or excessive adhesion formation.

Mean bowel wall thickness ($n = 5$) measured in unoperated bowel was measured as 4·3 mm for stomach, 2·0 mm for ileum, and 1·6 mm for caecum. Calculations for individual load–extension curves (all intestinal wounds, stapled and sutured) are summarized in *Table 1*. Supplemental EGF increased breaking strength (F_{max}) but there was no measurable change in maximum tensile strength or the modulus of elasticity.

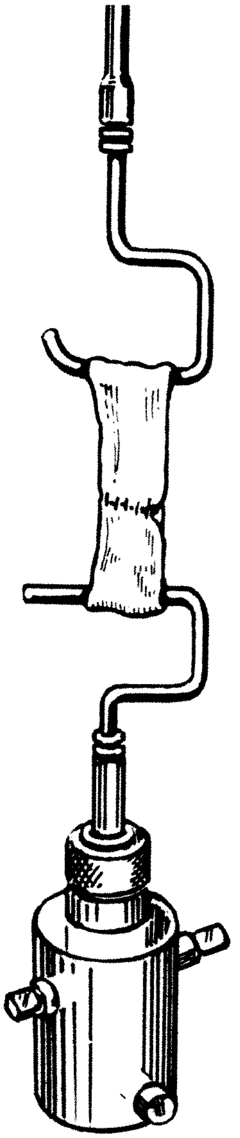

Figure 1 *A 20-mm segment of bowel wall was mounted on hooks between the lower fixed clamp and the movable cross-head of the tensiometer. The sutured surgical incision is oriented in the longitudinal axis of the bowel walls*

Histological examination of the anastomotic site showed organizing granulation tissue with fresh fine collagen fibrils: in the EGF-treated animals the area was more cellular than in the controls, showing an increase in fibroblasts, endothelial cells and macrophages (*Figure 3*). Collagen deposition also appeared to be increased (*Figure 4*).

Discussion

The intestinal wall is a composite structure of smooth muscle, collagen, elastin, reticular fibres and cellular and nerve elements. The main load-bearing material from which the intestinal wall derives its tensile strength is, however, mature polymerized collagen[11,12]. In these experiments, the load–extension curve before rupture is almost linear indicating that the collagen fibres are undergoing linear extension, and the stress recorded at rupture is a measure of collagen fibre strength in the submucosa. The tensile strength attained after 5 days in both groups occurs in spite of residual inflammation, oedema, cellular infiltration and apparent degree of disorganization of collagen. Collagen fibrils within this mass of active granulation tissue were increased in the treated group suggesting a basis for the increase in wound strength. The maturation of collagen fibrils could be attributed to a reduction in collagenase activity induced by EGF. Persistent collagenase activity in wounds impairs strength in the early phase of healing[13,14].

Five days after wounding is the optimal time to study tensile strength in the intestinal wall. Our pilot studies confirmed the results of other investigators which demonstrated that the strength in intestinal wounds decreases until day 3 or 4; collagen content parallels this decrease in strength which occurs in spite of increased collagen synthesis and is probably due to increased collagenolysis. After 7 days, collagen content and tensile strength have reached supranormal levels and specimens subjected to tensile tests rupture at sites distant from the wound area[15,16]. Between days 3 and 7, therefore, collagen content remains static, collagenase activity is decreasing, and tensile strength is increasing. Our studies indicate that EGF accelerates this early increase in tensile strength but the mechanism remains obscure. Maximum tensile strain and modulus of elasticity were unchanged by EGF but these measurements may not accurately reflect the physical property of a biomaterial such as collagen[17]. A more sensitive test might register a change in these two parameters indicating a change in the physical characteristics of the collagen induced by EGF.

Measurement of tensile strength across a longitudinal wound in the bowel wall is analogous to measurements of tensile strength across a transverse or anastomotic wound[18]. The methods used in our experiments for tensile strength measurement are derived from Watters' technique for examining colonic segments[19]. The advantage is a highly standardized technique avoiding the use of mechanical clamps which invariably damage bowel wall giving misleading results.

Table 1 *Comparison of properties of load–extension curves for intestinal wounds in EGF-treated and untreated pigs*

	EGF (0·5 μg kg^{-1} 24 h^{-1}) ($n = 8$)			Untreated ($n = 8$)		
	Stomach	Ileum	Colon	Stomach	Ileum	Colon
Breaking strength (F_{max}, g mm^{-2})	32·4(2·2)*	56·8(5·4)*	96·0(3·8)†	28·0(2·0)	46·8(4·8)	85·6(4·2)
Maximum tensile strain (% elongation)	205(43)	167(38)	202(31)	230(58)	172(45)	236(27)
Modulus of elasticity	53(8)	42(10)	68(7)	61(10)	37(8)	73(6)

Values are mean(s.d.); EGF, epidermal growth factor; * $P < 0·05$; † $P < 0·01$ (EGF *versus* untreated)

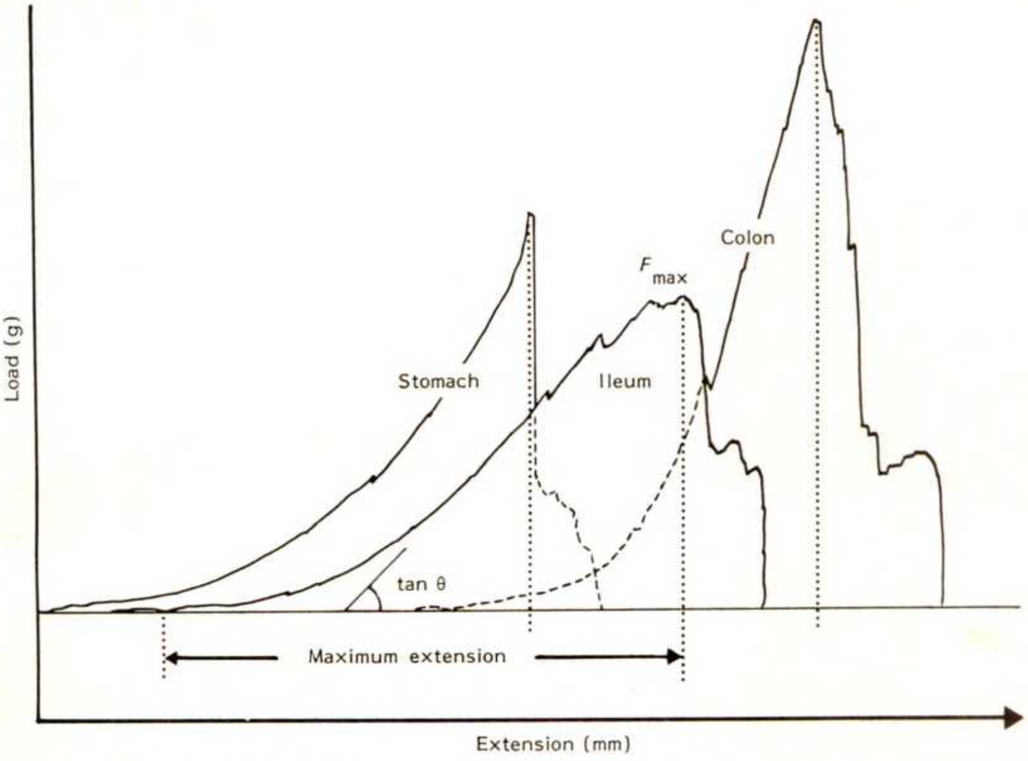

Figure 2 *Typical load–extension curves for stomach, ileum and colon enabling calculation of breaking strength* (F_{max}), *maximum tensile strain (percentage elongation) and modulus of elasticity (related to tan θ)*

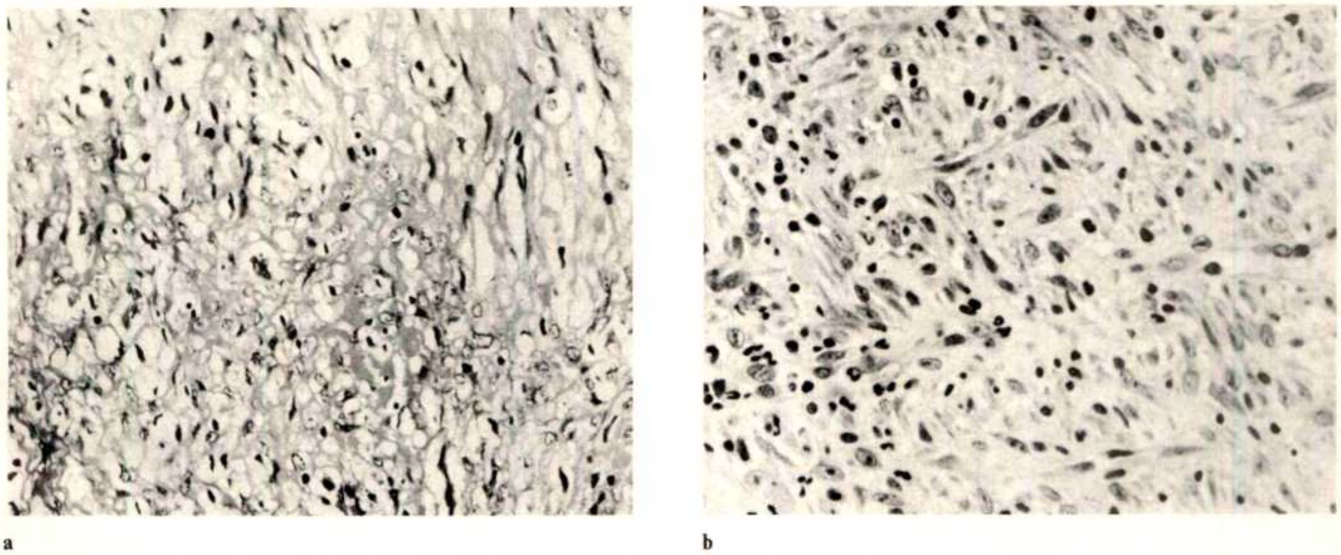

Figure 3 *Detail (× 460) of the anastomotic site, showing increased cellularity in the organizing granulation tissue:* **a** *untreated,* **b** *treated*

A number of growth factors and cytokines have been described which regulate wound repair, wound cell migration and collagen synthesis[20–24]. In the intestinal wounds of pigs, polymorphs were somewhat increased, whereas macrophages, endothelial cells and fibroblasts were markedly increased by treatment. Thus EGF not only accelerated the migration of cells into the wound area but also stimulated early synthesis of collagen. The cellular response to wounding in intestine is similar to that in skin but the timing of events and final outcome are dissimilar indicating that regulatory factors may differ. Our results show that EGF is one such factor and represents another possible application for the clinical use of peptide growth factors[25].

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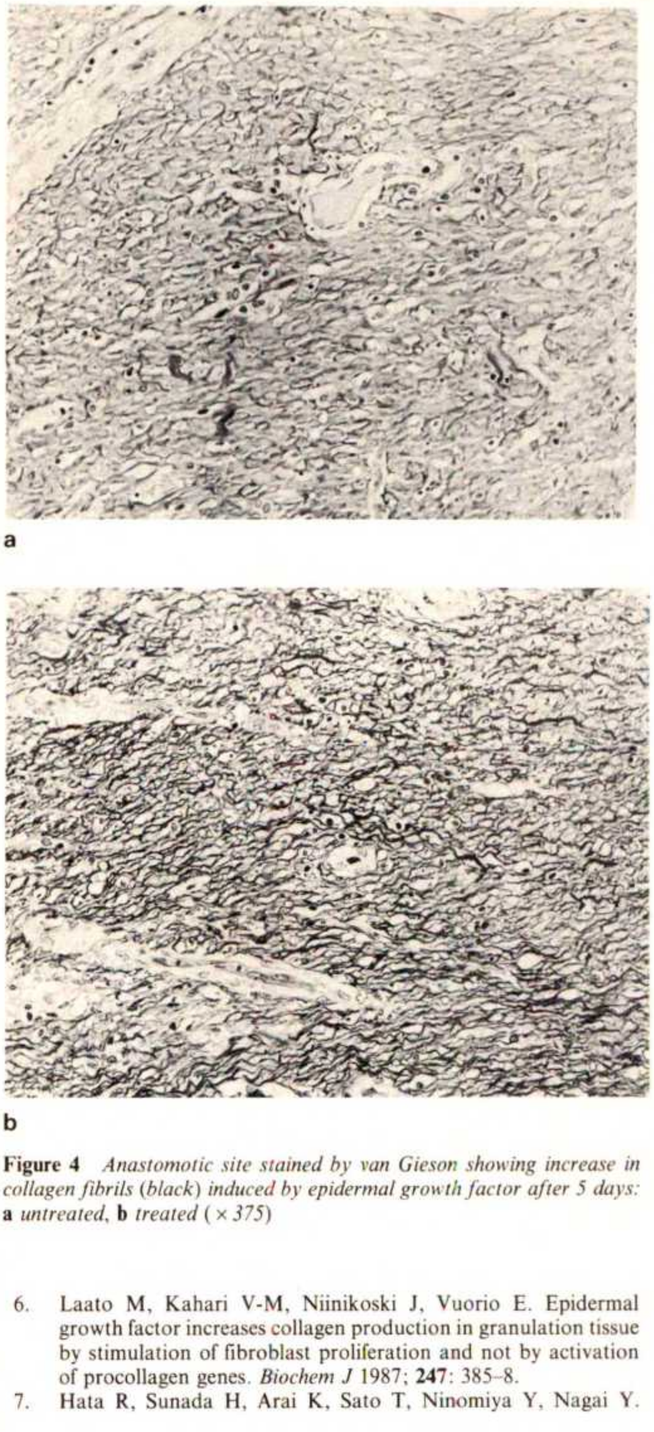

Figure 4 *Anastomotic site stained by van Gieson showing increase in collagen fibrils (black) induced by epidermal growth factor after 5 days:* **a** *untreated*, **b** *treated* (× *375*)

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Nitrogen requirements in severely injured patients

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The study was designed to evaluate nitrogen needs in severely injured patients during the first week after trauma. Thirty-nine patients aged from 18 to 65 years with a burn or fractures of more than two long bones were studied. Energy requirements were given parenterally as fat and glucose in isocaloric amounts. The patients were randomized into five groups receiving different amounts of nitrogen from zero to 0·3 g kg body-weight^{-1} 24 h^{-1}. Daily and cumulative nitrogen balance, urinary 3-methylhistidine excretion and nitrogen retention were calculated on days 2–8 after trauma. With no nitrogen, the mean(s.e.m.) daily nitrogen balance after the trauma was $-13{\cdot}8(0{\cdot}5)$ gN. The balance improved markedly in groups with a nitrogen intake of up to 0·2 g kg body-weight^{-1} ($P<0{\cdot}001$) compared with the no-nitrogen group. The 3-methylhistidine excretion increased because of the trauma in all groups with no statistically significant difference between the groups. Nitrogen retention decreased with increase in nitrogen supply and with time after injury. It is suggested that a nitrogen supply of 0·20 kg body-weight^{-1} 24 h^{-1} is optimal for severely injured patients during the first week after trauma.

Keywords: Nitrogen requirements, multiple trauma, burns

Severe trauma produces striking metabolic changes, with an increased resting energy expenditure and an increased nitrogen excretion with a negative nitrogen balance[1,2]. The nitrogen balance is influenced by protein and energy intake[3,4] and is a function of whole body protein synthesis and degradation.

In hypermetabolic patients without protein support, nitrogen losses of 25–30 g day^{-1} commonly occur[5,6]. In these patients nitrogen supply is considered an important aspect of parenteral nutrition to improve wound healing and resistance to infection, and to counteract protein wasting. It seems impossible, however, to maintain nitrogen balance in hypermetabolic patients, probably because of a block in protein synthesis in the skeletal muscle[7]. The optimal amount of protein that can be utilized mainly for protein synthesis remains controversial.

This study examines the influence of different nitrogen intakes with constant and adequate energy supply on protein metabolism after burn or fracture injury.

Patients and methods

Thirty-nine patients, aged from 18 to 62 years, with a burn injury (mean burn area 39/25 expressed as total/full skin in percentage of body surface) or fractures of more than two long bones were included in the study. Body-weight was between 60 and 80 kg. The patients were previously healthy and without systemic disease. Patients with head injury or severe kidney and liver function disturbance were excluded.

On admission the patients were resuscitated with Ringer lactate solution, albumin and concentrated red cells according to need, and initial surgical procedures were performed before the study. Patients who were in a stable condition on the morning of the day after the accident were randomized to receive different parenteral nutrition regimens.

Energy was supplied (45–50 kcal kg body-weight^{-1}) as fat (Intralipid®, KabiVitrum, Stockholm, Sweden) and glucose in isocaloric amounts. Various nitrogen intakes (*Table 1*) of 0, 0·1, 0·2, 0·25 and 0·3 g kg body-weight^{-1} 24 h^{-1} (Vamin®, KabiVitrum) were used. Total parenteral nutrition was given from day 2 to day 8 via a central venous catheter. Electrolytes, vitamins and trace elements were included. Glucose was given continuously, and fat and amino acids were administered between 10.00 hours and midnight.

Consecutive 24-h urine samples and all aspirates and faeces were collected for 7 days from the morning of day 2, and blood samples were collected on the morning of days 2, 4 and 8 after entry into the study.

Blood glucose concentration was determined by a routine hexokinase method. Serum albumin, urea and creatinine were measured using an automatic analyser (Smac, Technicon, New York, USA).

Urine, faeces, drain fluids and gastric juice were analysed for total nitrogen content using a semi-micro Kjeldahl method[8]. The nitrogen balance was calculated as the difference between the intake of nitrogen and the urinary, faecal and exudate losses of nitrogen for each day. Other losses, for example from skin, were not taken into account. A correction of the nitrogen balance was made for changes in the total urea pool assuming the total body water to be 60 per cent of body-weight in men and 55 per cent in women[8].

The percentage nitrogen retention was calculated from the change in nitrogen balance and actual increase in nitrogen intake. The calculations were based on the differences between the group receiving no nitrogen supply and the different groups receiving nitrogen on days 2–3, 4–5 and 6–8 according to the following formula:

$$\text{Nitrogen retention} = \frac{NB_x - NB_0}{I}$$

where NB_x = mean nitrogen balance (g N) on days 2–3, 4–5, 6–8 in the different groups receiving nitrogen; NB_0 = mean nitrogen balance (g N) on days 2–3, 4–5 and 6–8 in the group with no nitrogen supply; and I = mean increase in nitrogen intake on days 2–3, 4–5 and 6–8 in the different nitrogen groups compared with the group receiving no nitrogen supply.

The urinary 3-methylhistidine excretion was measured by an amino acid analyser (Kontron, Basel, Switzerland).

Table 1 *Clinical data on the different nutritional groups*

	Nitrogen intake (g kg body-weight^{-1} 24 h^{-1})				
	0	0·1	0·2	0·25	0·3
No. of patients	9	8	7	8	7
Sex (male:female)	6:3	7:1	5:2	6:2	4:3
Mean age (years)	38	41	37	44	45
Patients with multiple trauma ($n=21$)	5	6	4	3	3
Patients with burns ($n=18$)	4	2	3	5	4
Patients on a ventilator ($n=12$)	3	2	1	3	3

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Excretion of nitrogen and of 3-methylhistidine in urine was related to creatinine excretion, correcting for incomplete urine collection and variability in muscle mass.

Muscle biopsies were taken from the lateral portion of the quadriceps femoris muscle on days 2, 4 and 8 after the trauma in all groups except the group receiving 0·1 g N kg body-weight^{-1} day^{-1}. The samples were immediately frozen by plunging the biopsy needle into liquid nitrogen. The samples were then freeze-dried, extracted and spectrophotometrically analysed for adenosine triphosphate (ATP)[9].

The nature, purpose and possible risks involved in the experimental procedures were explained to the patients before obtaining their voluntary consent. The research protocol was accepted by the local ethical committee.

All statistical calculations were performed using an ABC 800 computer (Luxor Company, Motala, Sweden). The results are presented as mean(s.e.m.). The significance of differences was determined using Student's *t* test and Wilcoxon's rank sum test for paired and unpaired values.

Results

Clinical data for the five groups are presented in *Table 1*. Twenty-one patients with multiple trauma and 18 patients with burns (mean 37 per cent of body surface area) entered the study. Twelve patients required ventilatory support and all patients survived.

On admission the mean body-weight ranged between 65 and 75 kg. There were no significant differences between the groups (*Table 2*). During the study period (day 8), the serum albumin level was below normal (29–33 g l^{-1}) and creatinine levels remained normal, while blood glucose concentrations were at the upper reference limit in all groups. There were no significant differences between the groups. Serum urea concentration on day 8 after the trauma was slightly increased in the groups receiving 0·2, 0·25 and 0·3 g N kg body-weight^{-1} 24 h^{-1}. ATP content in muscle tissue was somewhat reduced (normal(s.e.m.) value 24·0(0·3)) in the studied groups, without any significant difference between the groups.

Nitrogen excretion in urine increased with increasing nitrogen intake (*Table 3*). In the groups receiving 0·2–0·3 g N kg body-weight^{-1} 24 h^{-1} more marked losses of nitrogen in urine were observed 4–8 days after initiation of the nitrogen supply. The creatinine excretion was unchanged in all groups throughout the study. The same pattern of nitrogen loss in urine was seen when nitrogen excretion was related to creatinine excretion.

Table 2 *Body-weight and biochemical parameters on days 2 and 8 after trauma in relation to nitrogen intake*

	Nitrogen intake (g kg body-weight^{-1} 24 h^{-1})				
	0	0·1	0·2	0·25	0·3
Body-weight (kg)					
Day 2	68·3(2·3)	74·5(4·2)	67·7(5·7)	76·0(2·4)	74·7(1·6)
Day 8	68·2(2·4)	73·5(4·2)	65·6(4·8)	73·2(3·6)	73·3(2·8)
Serum albumin (g l^{-1})					
Day 2	36·2(1·4)	30·8(1·2)	33·3(1·6)	30·1(1·0)	32·2(1·3)
Day 8	32·9(1·2)	28·8(1·6)	31·2(1·7)	28·3(0·6)	31·3(1·4)
Blood glucose (mmol l^{-1})					
Day 2	7·9(0·7)	7·3(0·5)	7·0(0·6)	9·4(0·8)	8·9(0·7)
Day 8	7·6(0·5)	6·3(0·2)	8·4(2·1)	10·3(1·2)	8·2(0·5)
Serum creatinine (mmol l^{-1})					
Day 2	84·2(5·7)	93·8(16·1)	80·6(10·5)	90·2(9·2)	83·4(4·8)
Day 8	80·8(6·9)	100·7(20·2)	95·1(11·1)	112·8(19·0)	103·3(13·9)
Serum urea (mmol l^{-1})					
Day 2	4·8(0·4)	4·9(0·9)	5·5(1·1)	4·8(0·4)	5·9(0·5)
Day 8	4·6(0·7)	7·1(1·3)	12·1(2·4)*	11·0(2·4)*	10·4(1·2)*
Muscle ATP (mmol kg^{-1} dry muscle)					
Day 2	24·4(1·7)	21·0(2·0)	22·5(0·9)	22·3(0·6)	23·5(0·9)
Day 8	21·0(2·1)	19·7(1·4)	19·3(1·7)	21·3(0·5)	19·7(0·5)

Values are mean(s.e.m.); ATP, adenosine triphosphate; * $P < 0·01$

Table 3 *Urinary excretion of nitrogen and creatinine and the ratios of 3-methylhistidine/creatinine and nitrogen/creatinine urinary excretion in relation to different nitrogen intakes*

		Nitrogen intake (g kg body-weight^{-1} 24 h^{-1})				
	Days	0	0·1	0·2	0·25	0·3
Urinary nitrogen (g 24 h^{-1})	2–3	12·7(1·07)	10·7(1·25)	14·5(1·56)	17·9(0·89)	22·3(0·93)
	4–5	12·7(1·09)	14·0(2·37)	16·3(1·74)	21·4(0·93)	28·4(1·13)
	6–8	14·3(1·44)	12·5(1·43)	23·3(3·20)*	25·1(1·46)†	30·7(1·47)*
Urinary creatinine (mmol 24 h^{-1})	2–3	16·8(1·47)	16·8(1·20)	11·6(1·11)	15·8(0·88)	16·8(0·73)
	4–5	15·7(1·40)	14·1(1·18)	12·0(0·81)	15·5(0·89)	15·8(0·73)
	6–8	14·5(1·13)	14·3(1·46)	13·6(0·88)	15·1(1·04)	14·8(0·71)
Ratio urinary 3-methylhistidine/ creatinine ($\times 10^3$)	2–3	35·6(10·2)	25·1(3·9)	24·2(2·7)	38·8(6·3)	28·7(2·1)
	4–5	39·8(4·7)	29·7(2·0)	24·7(2·4)	33·4(3·0)	30·8(2·7)
	6–8	31·6(4·2)	25·3(3·9)	28·3(3·9)	33·0(2·7)	32·9(1·9)
Ratio urinary nitrogen/creatinine	2–3	58·1(8·2)	49·9(7·3)	85·8(11·0)	88·3(4·9)	97·7(5·0)
	4–5	62·0(7·6)	70·8(10·3)	98·8(10·4)	102·8(5·6)*	131·3(5·4)‡
	6–8	67·4(8·3)	62·1(1·0)	133·4(16·5)*	125·7(6·5)‡	151·3(8·2)‡

Values are mean(s.e.m.); the ratios are based on molar weights; * $P < 0·05$; † $P < 0·01$; ‡ $P < 0·001$

The mean nitrogen balance for each day in all groups showed a negative balance during the first week after the injury. With no nitrogen supply the mean(s.e.m.) daily nitrogen balance during the first week was −13·8(0·5) g N (*Figure 1*). The balance was, however, markedly improved with a daily supply of 0·1 g N kg body-weight^{-1} ($P<0·001$) and was further improved in the group receiving 0·2 g N kg body-weight^{-1} 24 h^{-1} ($P<0·001$) compared with the no-nitrogen group. The improvement plateaued at 0·2–0·25 g N kg body-weight^{-1} 24 h^{-1}. The cumulative nitrogen balance after 7 days of nitrogen supply showed a marked improvement in the group receiving 0·1 g N kg body-weight^{-1} 24 h^{-1} ($P<0·01$; *Figure 2*).

Excretion of 3-methylhistidine in urine was increased in all groups, with no significant difference between the groups (*Table 3*). When 3-methylhistidine excretion was related to creatinine excretion, the same results were seen.

In urine, excretion of urea increased significantly in relation to total nitrogen excretion when nitrogen was given (*Table 4*). More than 90 per cent of the total nitrogen excretion consisted of urea-nitrogen. Nitrogen retention diminished with increasing amounts of supplemented nitrogen (*Table 4*).

Discussion

The five groups with different nitrogen intake were comparable with respect to body-weight, sex and age, and the clinical course did not differ between groups. There were some differences in the number of burned and multiple trauma patients in the groups which might have affected nitrogen balance calculations due to difficulty in estimating losses through the skin. Also, there may have been an accumulation of nitrogen in tissue oedema which could affect results in the burned patients[10]. Serum albumin, blood glucose and muscle ATP all indicated a similar metabolic response to the injury.

Serum urea showed a tendency to increase within reference limits if the nitrogen supply exceeded 0·1–0·2 g kg body-weight^{-1} 24 h^{-1}. In the absence of renal insufficiency an increasing serum urea and a normal creatinine level indicate catabolism and partial utilization of supplied amino acids as substrates for gluconeogenesis.

When evaluating nitrogen excretion it is important to control energy intake. It has been shown in depleted patients that an additional 1 kcal of energy spared 1·2 mg N at a nitrogen intake of 160 mg kg^{-1} 24 h^{-1} (Reference 11). Our earlier studies showed an increased energy need corresponding to an energy intake of 40–45 kcal kg^{-1} 24 h^{-1} (Reference 10). We therefore determined that in the present study the patients would be in caloric balance[10]. Because different kinds of energy source such as fat and carbohydrates influence results[12–14], all patients received equal caloric amounts of fat and glucose.

The most important finding in the present study was the improved daily nitrogen balance in patients given a nitrogen supply of up to 0·2 g kg body-weight^{-1} 24 h^{-1}. A further increase in nitrogen supply did not improve the nitrogen balance. Nitrogen retention of 70 per cent occurs when the daily nitrogen intake is increased from zero to 0·2 g kg body-weight^{-1}. Further retention of nitrogen was not seen for a nitrogen intake of between 0·2 and 0·3 g kg body-weight^{-1} 24 h^{-1}. In severely burned patients, Wolfe *et al.*[15] studied the influence of two levels of protein intake, 2·2 and 1·4 g kg^{-1} 24 h^{-1}, on protein metabolism. Leucine kinetics were analysed by an infusion of [^{13}C]leucine. The data indicated that an optimal balance between protein synthesis and degradation could be reached with a protein intake of 1·4 g kg^{-1} 24 h^{-1} which is equivalent to about 0·2 g N kg^{-1} 24 h^{-1} and in accordance with our data.

Shaw *et al.*[16] studied the nitrogen retention in a group of malnourished, non-stressed patients and demonstrated that an

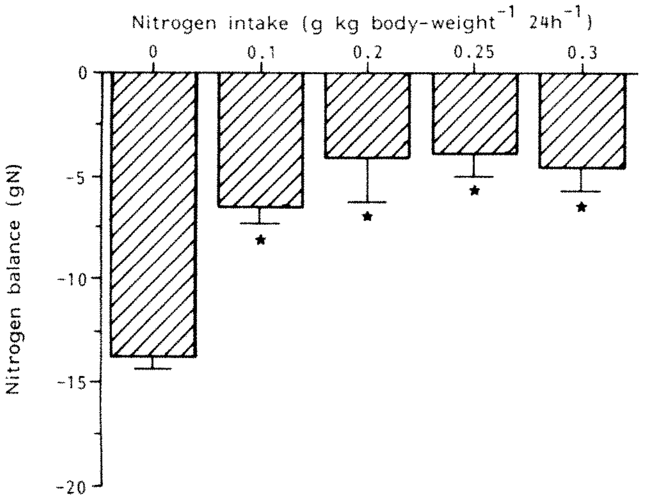

Figure 1 *Mean (s.e.m.) daily nitrogen balance on days 2–8 after severe trauma. The groups receiving nitrogen are compared with the group with no nitrogen intake.* * $P<0·001$

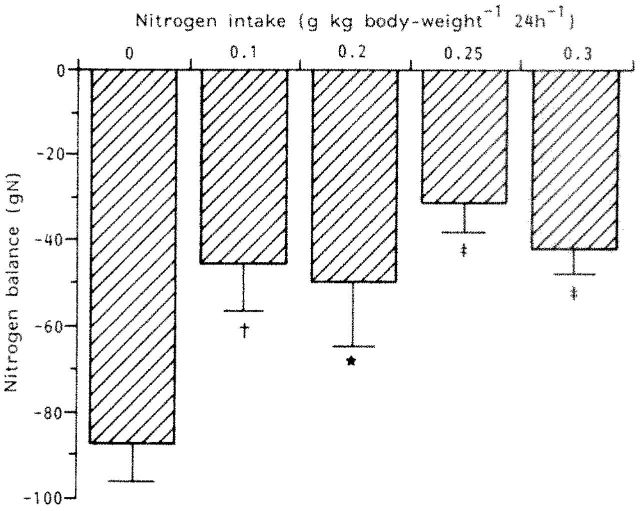

Figure 2 *Mean (s.e.m.) cumulative nitrogen balance on day 8 after trauma. The groups receiving nitrogen are compared with the group with no nitrogen intake.* * $P<0·05$; † $P<0·01$; ‡ $P<0·001$

Table 4 *Ratio between urinary urea and total nitrogen excretion in relation to different nitrogen intakes*

		Nitrogen intake (g kg body-weight^{-1} 24 h^{-1})				
	Days	0	0·1	0·2	0·25	0·3
Ratio urinary urea/nitrogen	2–3	0·76(0·05)	0·91(0·03)	0·90(0·04)	0·91(0·02)	0·92(0·03)
	4–5	0·79(0·04)	0·98(0·04)	0·93(0·03)	0·92(0·02)	0·91(0·03)
	6–8	0·78(0·02)	0·96(0·04)	0·98(0·04)	0·92(0·03)	0·93(0·02)
Nitrogen retention (%)	2–3	–	78·2(13·07)	89·3(15·77)	76·4(6·21)	68·8(5·98)
	4–5	–	61·5(16·47)	75·6(10·35)	55·4(4·44)†	43·7(3·72)†
	6–8	–	66·7(17·47)	38·7(15·86)*	44·5(5·39)‡	27·1(3·44)‡

Values are mean(s.e.m.); nitrogen retention was compared with the group with no nitrogen intake; * $P<0·05$; † $P<0·01$; ‡ $P<0·001$

increase from a low to a high nitrogen diet (a difference of 40 mg N kg^{-1} 24 h^{-1}) caused a 21 per cent retention of the increased nitrogen intake. Further studies in malnourished patients requiring total parenteral nutrition have revealed that the rate of protein synthesis increased up to a level of nitrogen supply of about 0·2 g kg^{-1} 24 h^{-1} (Reference 17). The results in severely injured patients suggest that the nitrogen-sparing effect of increasing amino acid supply may be related to the degree of hypermetabolism and the condition of the patient. Some weeks after the trauma, in the more anabolic phase, an increasing supply of nitrogen might further improve the nitrogen balance. At the moment no data are available to support this theory.

Excretion of 3-methylhistidine in urine was increased two to three times in all patients, indicating an increased protein degradation[4,18]. The 3-methylhistidine excretion was negatively related to the nitrogen balance, pointing to an inhibitory effect on protein degradation by increasing the amount of nitrogen intake. This does not correspond with the small effect on nitrogen balance observed by increasing the daily nitrogen intake above 0·1–0·2 g kg body-$weight^{-1}$ 24 h^{-1}. The possible cause of the decreased 3-methylhistidine excretion by an improved nitrogen balance might be explained by an effect of protein in the gastrointestinal tract.

In the future it will be important to study different organs to evaluate the effect of nutritional supply during various phases after trauma. In the early period after severe trauma, the hypermetabolic phase, a nitrogen supply of up to 0·2 g kg body-$weight^{-1}$ 24 h^{-1} seems to be optimal.

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Urine acid output as a test of completeness of vagotomy

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Peak acid output in response to sham feeding and changes in urine acid output 2 and 3 hours after a test meal have been measured in 20 normal volunteers, 17 asymptomatic patients after vagotomy, six patients with recurrent duodenal ulcer after vagotomy and ten normal subjects given a 48-h course of ranitidine, 150 mg 12-hourly. Gastric peak acid output in normal volunteers ranged from 6·9 to 22·1 mmol/h. All asymptomatic patients after vagotomy had a peak acid output <7 mmol/h, consistent with complete vagotomy. Five patients with recurrent ulcer had a peak acid output >8 mmol/h, suggesting an incomplete vagotomy. Urine acid output after a test meal, expressed as the change from the basal rate of acid output, was always in a negative direction in normal subjects (fall in acid output = postprandial alkaline tide). This change was abolished in patients with complete vagotomy, in whom urine acid output increased after a meal. In five patients with incomplete vagotomy (and one other with recurrent ulcer and unknown vagal status) the urine acid output changed in a negative direction after a test meal. The relationship of urine acid output to gastric secretion was confirmed by the abolition of the postprandial alkaline tide in normal subjects given ranitidine. The results in patients with incomplete vagotomy did not overlap with those from patients with complete vagotomy. This suggests that this test could be used for the routine postoperative assessment of completeness of vagotomy.

Keywords: Gastric secretion, gastric function tests, vagotomy, sham feeding

After vagotomy for duodenal ulcer, recurrent ulceration is more likely if the vagotomy is incomplete[1]. In the patient with a recurrent ulcer, assessment of the vagal innervation of the stomach may help to plan further management[2]. Routine postoperative assessment of the completeness of vagotomy could be used as a means of quality control, in which the surgeon received information shortly after surgery about the accuracy of his technique.

Until now, tests of vagal innervation of the stomach have required nasogastric intubation. The original Hollander test required, in addition to nasogastric aspiration, injection of sufficient insulin to produce symptomatic hypoglycaemia. This was unpleasant, and occasionally dangerous for the patient[3,4]. More recently, modified sham feeding, by the 'chew and spit' method has been advocated[5,6]. This method is as accurate as the insulin test for the detection of incomplete vagotomy, but avoids the dangers of hypoglycaemia[7–9]. Both of these techniques require nasogastric intubation and aspiration of gastric secretion. This requirement is a major impediment to the widespread adoption of routine assessment of the completeness of vagotomy.

We have recently shown that there is a linear inverse relationship between the secretory capacity of the stomach, measured by standard gastric function tests, and the urine acid output after a test meal[10]. This relationship is a quantitative expression of the 'postprandial alkaline tide' which has been known to physiologists for many years. We have investigated this relationship further, in normal subjects and in patients after vagotomy, to determine whether postprandial changes in urine acid output could be used as a screening test for completeness of vagotomy.

Patients and methods

Patients

Four groups of subjects were studied.

Group 1. Twenty normal subjects aged 21–82 years were studied. There were 12 men. Eight were volunteer medical students and 12 were selected from surgical records on the following criteria: fully recovered from a repair of an inguinal hernia, and age and sex matched with a patient in the postvagotomy group.

Group 2. Seventeen patients aged 21–82 years were studied 1–18 years after vagotomy. There were 12 men. The type of vagotomy performed was truncal vagotomy and gastrojejunostomy (two patients), selective vagotomy and antrectomy (seven patients), and highly selective vagotomy without drainage in eight patients. None of these patients was taking H_2-receptor antagonists and none had any symptom of recurrent ulcer.

Group 3. Six patients aged 31–75 years with endoscopically-proven recurrent duodenal ulcer after vagotomy were studied. Five were men. Studies were performed 2–8 years after vagotomy: selective vagotomy and gastrojejunostomy in two patients, highly selective vagotomy in four patients.

Group 4. Ten normal volunteers (five were men; aged 18–48 years) were studied after suppression of gastric acid secretion with ranitidine 150 mg twice daily for 48 h. The last dose was taken on the morning of the test.

The subjects were instructed to fast from midnight and to abstain from smoking for 48 h before the test. Patients with recurrent ulcer were asked to discontinue antisecretory drugs 48 h before the test. Groups 1, 2 and 3 were studied on two occasions, one for sham feeding and one for the test meal. Group 4 (normal volunteers on ranitidine) was studied only after a test meal.

Methods

Sham feeding. With the subject in a semi-recumbent position one

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Based on a paper presented to the Surgical Research Society, Newcastle upon Tyne, 6–7 July 1989

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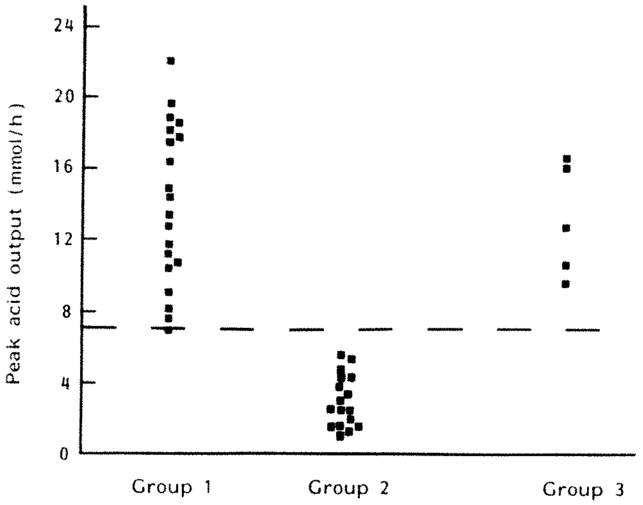

Figure 1 *Peak acid output during the first h after sham feeding. Group 1, normal volunteers; group 2, asymptomatic patients after vagotomy; group 3, patients with recurrent duodenal ulcer after vagotomy*

Table 1 *Changes in urine output from basal levels 2 and 3 h after sham feeding and after a test meal*

	Urine output, median (range)		
	Group 1 (mmol/h)	Group 2 (mmol/h)	Group 3 (mmol/h)
Sham feed			
after 2 h	−2·7 (−6·2 to −0·9)	−0·7 (−4·9 to +4·1)	−2·2 (−4·8 to −1·4)
after 3 h	−2·8 (−5·8 to −1·1)	0 (−8·7 to +5·7)	−0·7 (−2·7 to −0·5)
Test meal			
after 2 h	−2·1 (−3·2 to 0)	1·1 (−0·2 to +6·7)	−1·0 (−3·6 to 0·9)
after 3 h	−4·0 (−8·4 to −0·4)	2·6 (−3·2 to +6·4)	−0·7 (−2·7 to −0·5)

nostril and the throat were sprayed with a solution of lignocaine (3 per cent). A double-lumen nasogastric tube was passed into the stomach and the resting juice was aspirated. Continuous suction was applied to the tube throughout the test. The position of the tube was assessed with a modified water recovery test[11]. Water (250 ml) was instilled through the tube and aspiration was performed immediately. Recovery of 230 ml of water indicated that the tube was in a satisfactory position.

After a basal collection over 30 min, modified sham feeding was done using the 'chew and spit' technique. The test stimulus was two slices of toast and marmalade (bread 60 g, butter 10 g, marmalade 30 g). This was freshly prepared in a room remote from the subject. A mouthful of the stimulus was chewed and savoured, and then spat out. The mouth was rinsed with water between mouthfuls. Stimulation was discontinued after 10 min. Gastric juice was collected continuously in 15-min fractions for 30 min before and for 1 h after the start of sham feeding. The nasogastric tube was then removed and 300 ml water was given by mouth.

Urine samples were collected at three points by voiding. A basal sample (US1) was collected a measured time after early morning voiding, just before the sham feeding. A second sample (US2) was collected 2 h after the beginning of sham feeding. One hour later a third sample (US3) was obtained.

Test meal. The subject ate a standard meal. This consisted of one low fat flavoured yoghurt (5 g/100 g protein, 0·9 g/100 g fat, 14·0 g/100 g carbohydrate); two cheese and tomato sandwiches consisting of two slices (60 g) of brown bread (8·9 g/100 g protein, 2·2 g/100 g fat, 44·7 g/100 g carbohydrate), 50 g of cheddar cheese (26 g/100 g protein, 43·5 g/100 g fat) and one tomato (0·9 g/100 g protein, 28 g/100 g carbohydrate); three plain digestive biscuits (9·8 g/100 g protein, 20·5 g/100 g fat, 66 g/100 g carbohydrate); one apple (0·3 g/100 g protein, 11·9 g/100 g carbohydrate) and two glasses of water.

A urine sample (UM1) was taken by voiding, just before the subject ate the meal. Two further samples were obtained at 2 h and 3 h after UM1 (UM2, UM3 respectively).

Chemical determination. The volume of each gastric aspirate was recorded and then the acid content was measured by autotitration to an end-point of pH 7·0 (PHM 62 standard pH meter, TTT60 Titrator, ABU 11 Autoburette, and TT 60 Titration Assembly from Radiometer, Copenhagen, Denmark). The pH meter employs a pH electrode, has provision for temperature compensation and gives direct readings by means of an electronic digital display.

The determination of the net urinary acid (or base) was obtained using the method of Jorgensen[12]. A 10 ml sample of urine was acidified with 1 ml of 0·1 M hydrochloric acid to liberate carbon dioxide from any bicarbonate present and to dissolve any deposit of phosphate. The mixture was then boiled to drive off the carbon dioxide and after dilution was titrated to pH 7·4 with 0·1 M sodium hydroxide in the presence of formaldehyde.

Calculations. Peak gastric acid response to sham feeding was calculated by doubling the sum of the two highest observed outputs.

Urinary acid output was calculated from acid concentration × volume. This was expressed as output per h. Changes in urinary acid output after stimulation were calculated by subtraction of the basal rate of secretion. A negative value indicated a more alkaline urine.

Statistical analysis. Results were expressed as median and ranges. The values observed in different groups were compared directly. Signifiance was assessed using the Kruskal–Wallis one way analysis of variance.

Results

Peak acid output

The median peak acid output after sham feeding (*Figure 1*) in normal subjects was 13·8 mmol/h (range 6·9–22·1 mmol/h). We accepted a level of 7 mmol/h as discriminating between patients with a complete vagotomy and those with incomplete vagotomy[9]. The asymptomatic postvagotomy patients all had a peak acid output below this level (median 2·6 mmol/h, range 1·2–5·6 mmol/h). In contrast, five patients with known recurrent ulcer after vagotomy had a peak acid output in excess of this level (median 12·9 mmol/h, range 9·9–16·6 mmol/h). One further patient with recurrent ulcer was unable to tolerate the nasogastric tube so no figure for peak acid output could be obtained.

Urine acid output

After sham feeding with gastric aspiration, there was a fall in urine acid output at 2 and 3 h (*Table 1*). This fall was abolished after vagotomy but persisted after incomplete vagotomy in patients with recurrent ulcer. These differences were highly statistically significant ($P < 0·001$) but there remained some overlap between the symptomatic and asymptomatic vagotomy patients (*Figure 2*).

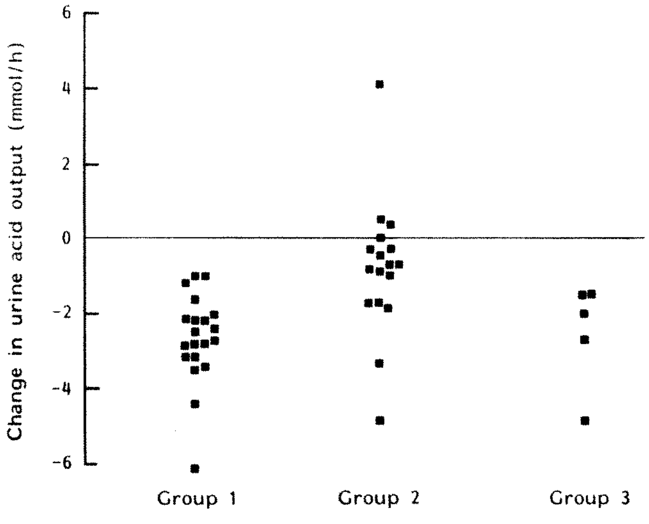

Figure 2 *Change in urine acid output 2 h after sham feeding. Group 1, normal volunteers; group 2, asymptomatic patients after vagotomy; group 3, patients with recurrent duodenal ulcer after vagotomy*

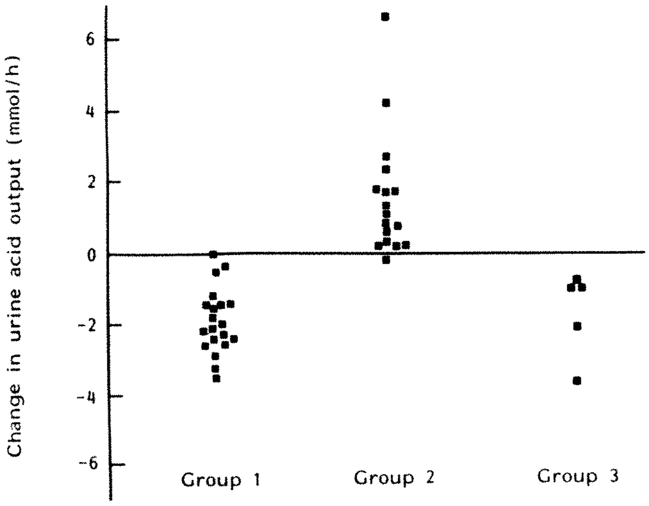

Figure 3 *Change in urine acid output 2 h after a test meal. Group 1, normal volunteers; group 2, asymptomatic patients after vagotomy; group 3, patients with recurrent duodenal ulcer after vagotomy*

After a meal, there was an even clearer separation between normal subjects, patients with complete vagotomy and those with recurrent ulcer. *Figure 3* shows the values obtained at 2 h after the meal. Similar findings were observed at 3 h, but there was rather more overlap between the groups (*Table 1*).

The changes in urine acid outputs after a meal in these three groups were again statistically significant ($P<0.001$). The patient with recurrent ulcer after vagotomy in whom it was not possible to obtain gastric function tests also had a fall in urine acid output after a meal (UM2 = −0·9 mmol/h) with a value in the normal/incomplete vagotomy range.

Urine acid output after a meal was measured in ten volunteers who were taking a short course of ranitidine. The normal fall in urine acid output after a meal was completely suppressed (UM2 median +1·2 mmol/h, range −0·9 to +2·9; UM3 median +0·1 mmol/h, range −1·2 to +2·5).

Discussion

We have investigated changes in urine acid output after a test meal in normal subjects and patients who have had a vagotomy. The test appears to be able to separate patients with incomplete vagotomy from those with a successful operation. This test avoids the dangers of insulin hypoglycaemia, and the discomfort of nasogastric intubation and so may become a useful screening test for the assessment of the results of operation.

Peak acid output after sham feeding in normal volunteers was similar to previously reported values[9,10]. This acid response to sham feeding was greatly reduced by vagotomy, in patients without symptoms. We found that all asymptomatic patients had a peak acid output <7 mmol/h, the critical value proposed by Athow *et al.*[9]. Conversely patients with recurrent ulceration all had a peak acid output in excess of this value, and so we conclude that these five patients had an incomplete vagotomy. There is controversy over whether correction of peak acid output for fluid movement across the pylorus, and for stature, is necessary to improve the discrimination of this test after vagotomy. In common with most authors[9,13] we accept the view[9] that such corrections are unnecessary. This view appears to be justified by the clear separation of values for peak acid output in asymptomatic vagotomy patients from those found in symptomatic patients and normal volunteers.

The postprandial alkaline tide has been well known for many years. Ahmad[14] suggested that measurement of pH of the urine after a meal could be a suitable screening test for completeness of vagotomy. We were unable to confirm this with our test meal[10] and again in the present study only a few normal subjects achieved a pH >7 in the postprandial urine samples. Indeed, half of the normal subjects showed no change in pH or a fall in pH (results not given). We believe that measurement of urine acid output is a much more sensitive indicator of changes in acid balance than is pH. Because the urine contains many buffers, there must be a considerable change in acid output before any significant change in pH occurs. We found considerable overlap of the changes in pH after a meal, in patients with complete and incomplete vagotomy, but there was no such overlap when urine acid output was measured.

We demonstrated significant differences between the changes in urinary acid output after sham feeding in the different groups (*Figure 2*) but these figures are of theoretical interest only. They confirm that the secretion and aspiration of gastric acid must be compensated for by an 'alkaline tide' in the urine. The fact that the differences between groups 2 and 3 were less clear than after a test meal may be a result of the smaller, shorter stimulus to gastric secretion with sham feeding.

Similar changes were seen in the urine acid output after the test meal (*Figure 3*), which is a finding of great practical interest. We found a complete separation of the responses of patients with complete vagotomy from those five patients with a proven incomplete vagotomy. There was no overlap between the changes seen after complete vagotomy and in normal subjects at 2 h after a meal. The demonstration of the persistence of the alkaline tide in the postprandial urine of patients with incomplete vagotomy leads us to propose this test as a sensitive indicator of complete vagotomy.

We accept that gastric secretion after a meal depends on factors other than vagal innervation, such as gastrin release and gastric distension. Nevertheless it is the predominance of the vagal effects which constitutes the rationale for the use of vagotomy in the management of duodenal ulcer. In our patients in whom residual innervation had been shown by the gastric acid response to sham feeding, the urine acid response to a meal was similar to that seen in normal subjects (*Figure 3*). In asymptomatic patients with complete vagotomy, confirmed by sham feeding, a test meal evoked no reduction in urine acid output. Thus the urine acid output after a test meal can separate patients with incomplete vagotomy from those with complete vagotomy, although other causes of increased gastric acid response to food could produce similar results.

Similar changes were observed in the urine collected 3 h after a meal. There was a wider range of values in all three groups and we feel that this 3-h urine sample is probably unnecessary to separate complete and incomplete vagotomy patients because sufficient information can be obtained with a sample taken at 2 h.

There was one patient with recurrent ulcer who was unable to tolerate a nasogastric tube. The values of the urine of this patient after a test meal also fell within the incomplete vagotomy range. This demonstrates another advantage of a urine test as opposed to gastric aspiration. Useful information was obtained in this patient in whom gastric intubation was impossible.

We confirmed the specific relationship between gastric acid output and changes in urine acid output in 10 normal volunteers given ranitidine. After a short course of this antisecretory agent, there was a complete suppression of the normal postprandial fall in urine acid output. We conclude that the changes seen in urine acid output after a meal are not dependent on any effect of vagotomy on gastric emptying or intestinal transit.

This study suggests that changes in urine acid output after a test meal can separate patients with recurrent ulcer after incomplete vagotomy from those with no symptoms after complete vagotomy. If these findings are confirmed this test will have two clinical applications. First, it may be useful in the assessment of patients with further symptoms or recurrent ulceration after vagotomy. By using this urine test as a screen, it may be possible to select patients for gastric aspiration tests and so spare some patients with normal postvagotomy responses the need to undergo nasogastric intubation. Second, it is clear that assessment of vagotomy in the postoperative period could be used as a method of quality control. We feel that this method has distinct advantages over the standard insulin hypoglycaemia or sham feeding tests. It is simple to carry out, does not require nasogastric intubation, and depends only on the assay of two samples of urine. These advantages may make it more widely useful than standard gastric function tests in the field of quality control.

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Announcement

International Hepato–Biliary Pancreatic Association

Frank Glenn Travelling Fellowship 1990

The International Hepato–Biliary Pancreatic Association invites applications for the above travelling Fellowship. A stipend of 5000 SFr is available to subsidize a young investigator in the field of hepato–biliary and pancreatic disorders. The applicant must be sponsored by a member of the Association. The stipend may be used to support a laboratory project and/or to subsidize travel expenses which are deemed appropriate to the field of investigations.

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Jejunal pouch reconstruction after total gastrectomy for cancer: experience in 29 patients

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The experience with interposed jejunal pouch after total gastrectomy for cancer in 29 patients is reviewed. There were two postoperative deaths (7 per cent) due, respectively, to myocardial infarction on day 5 and massive haemorrhage from the splenic vein on day 14. Anastomotic leaks, all from the proximal anastomosis, were encountered in three patients (11 per cent). These consisted of one minor clinical leak in a stapled anastomosis and two radiological leaks from hand-sutured anastomoses. Obstruction of the pouch or its conduit by recurrent tumour was not observed in any patient, including those who died from metastatic disease. There was one instance of benign stenosis of the distal anastomosis to the duodenum which required revisional surgery. The symptomatic assessment in the long-term surviving patients was good except for mild oesophagitis due to bile reflux in five patients. Body-weight was maintained and adverse nutritional consequences were not observed.

Keywords: Total gastrectomy, gastric cancer, jejunal pouch interposition, symptomatic and nutritional outcome

During the past decade there has been an increasing tendency to undertake total gastrectomy for gastric cancer, especially of the diffuse variety. The reasons for this include a more aggressive surgical approach aimed at achieving adequate tumour-free margins together with extended lymphadenectomy[1–8], and an increasing incidence of proximal gastric cancer[9,10] for which the appropriate operation is a total gastrectomy. A survival advantage emanating from the use of this aggressive approach has been reported in Japan[1–4] although the proof for the benefit of extended lymphadenectomy requires confirmation by prospective trials. In this continuing debate, the question of reconstruction has been overlooked, possibly because the majority of these patients have a short life expectancy and are generally believed, without much evidence, to be less prone to postcibal symptoms than patients undergoing gastric resections for ulcer disease.

The satisfactory long-term outcome of the jejunal pouch interposition introduced by the author as a remedial procedure in patients with the small stomach syndrome[11] or after completion gastrectomy for intractable symptoms has encouraged its use for reconstruction after total gastrectomy for cancer in those patients in whom the resection was considered to be potentially curative using the criteria of the Japanese Research Society for Gastric Cancer Study[12].

Patients and methods

A total of 29 patients undergoing R_2, R_3 total gastrectomy for gastric cancer have had an interposed jejunal pouch as the reconstructive procedure. The details of the patients are shown in *Table 1*. The follow-up has varied from 1 to 11 years with a median duration of 4·2 years. All resections were considered potentially curative at the time of surgery. However, on review of the pathological examination of the resected specimens, 12 patients had an 'absolute curative operation' where the R resection level exceeded the level of nodal involvement as defined by the Japanese Research Society, and 17 patients had a 'relative curative operation' when the nodal involvement equalled the R resection level.

Reconstruction

The technique used is similar to that previously described[11] but has been modified with increasing experience. All the anastomotic suture lines were performed using a single-layer deep seromuscular technique with interrupted 3/0 braided nylon or silk sutures except in three patients where the anastomosis of the pouch to the oesophagus and of the isoperistaltic conduit from the pouch to the duodenum were stapled.

The pouch is constructed from an isoperistaltic segment of upper jejunum. Selection of the segment is important and depends on the anatomy of the mesenteric arcades. The segment is based on a straight vascular pedicle consisting of a single artery and vein. The vascular pedicle is selected distal to the first two jejunal branches. The length of the isolated loop depends on the width of the subcostal angle and the build of the patient, and varies from 30 to 50 cm. Identifiable proximal and distal marker sutures are placed to ensure orientation and to avoid torsion of the vascular pedicle. After transection, the isolated loop is wrapped in a moist warm pack until restoration of small bowel continuity below the graft is completed by means of an end-to-end anastomosis. The proximal end of the isolated jejunal loop is then closed by simple invagination and interrupted seromuscular sutures. The loop is then folded on itself such that the open limb (distal) is longer than the closed one by some 5·0 cm. An enteroenteric anastomosis is then effected between the two adjacent loops. It is important to leave a gap wide enough to admit the index finger between the proximal end of the anastomosis and the apex of the folded loop (*Figure 1*). This greatly facilitates the proximal anastomosis and avoids a T-shaped suture line which is intrinsically weak. The external wall of the closed lower loop is then sutured to the adjacent conduit (*Figure 2*). This prevents sagging and possible blind loop formation and imparts a semicircular infolding

Table 1 *Details of 29 patients undergoing radical total gastrectomy with reconstruction by an interposed jejunal pouch*

Sex (F, M)	11 18
Median age in years (range)	71 (51–83)
Tumour type	
Intestinal	17
Diffuse	12
pT	
T_1	2
T_2	21
T_3	6
pN	
N_0	2
N_1	27
N_{1+2}	17
N_{1+2+3}*	3

* N_3 is now considered as distant metastases in the new agreed staging[13]

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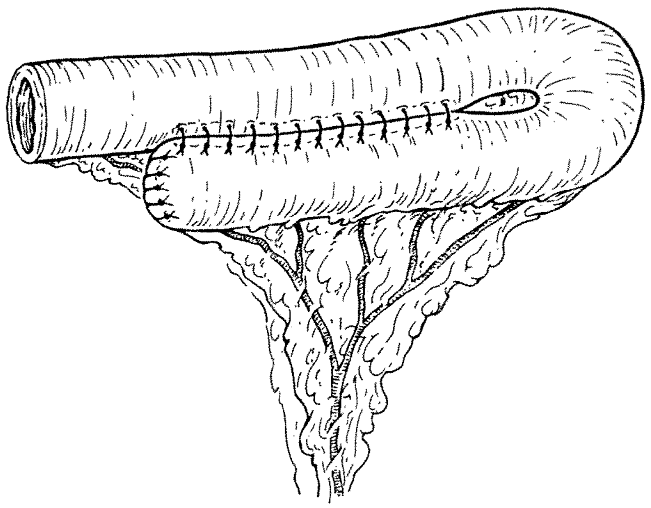

Figure 1 *Enteroenteric anastomosis between the adjacent limbs of the isolated segment of jejunum leaving a small gap between the suture line and the apex of the folded loop. The extra 5·0 cm length of the distal limb forms the conduit from the pouch*

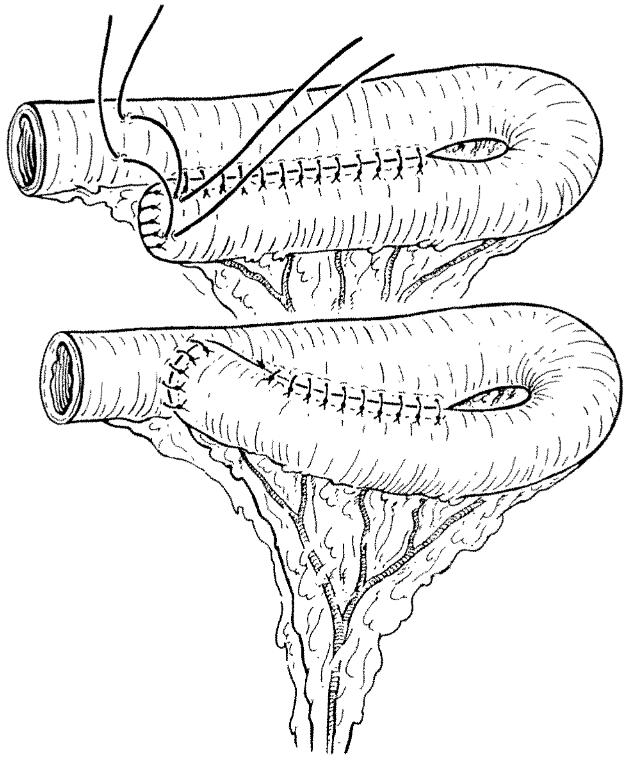

Figure 2 *Seromuscular sutures between the outer wall of the closed loop to the adjacent conduit to prevent sagging and blind loop formation*

The completed pouch is then transferred to the supracolic compartment through a small gap in the transverse mesocolon to the left of the middle colic vessels. Care is taken to avoid twisting of the mesenteric pedicle during this manoeuvre. An incision of 2·5–3·0 cm is then made at the proximal end of the pouch for anastomosis to the oesophagus. Finally the isoperistaltic conduit from the pouch is sutured end-to-end to the duodenum (*Figure 3*). The completed pouch assumes a curved disposition rather similar to that of the normal stomach (*Figure 4*).

The proximal and distal anastomoses were stapled in three patients. The pouch was constructed as described above except that the anterior wall of the enteroenteric anastomosis was left partially unsutured to allow insertion of the Ethicon (Ethicon, Edinburgh, UK) (two patients) or Autosuture (US Surgical Corporation, Norwalk, Connecticut, USA) (one patient) circular stapler. Purse-string sutures using 2/0 Prolene® (Ethicon Ltd.) were inserted at the ends of the cut oesophagus, the end of the conduit and the duodenal stump. The end of the stapler was removed for the proximal anastomosis and the central rod of the gun was used to perforate the apex of the pouch. The fully assembled gun was introduced into the pouch and conduit for the distal anastomosis to the duodenal stump. After the stapling was completed, the pouch was closed with interrupted deep seromuscular sutures. In practice, the author has not found any advantage in the use of stapling over hand-suturing for the construction of these pouches except for the high anastomosis when the lower 5–7 cm of the oesophagus is removed for tumours encroaching on the gastro-oesophageal junction. Division of the right crus facilitates the anastomosis in these patients.

Results

Postoperative morbidity and mortality

There were two postoperative deaths: one due to myocardial infarction on day 5 and the other to massive haemorrhage from the splenic vein on day 14. Anastomotic leaks, all from the proximal anastomosis, were encountered in three patients (11 per cent). These consisted of one minor clinical leak from a stapled anastomosis and two radiological leaks from hand-sutured anastomoses. The former declared itself subsequent to

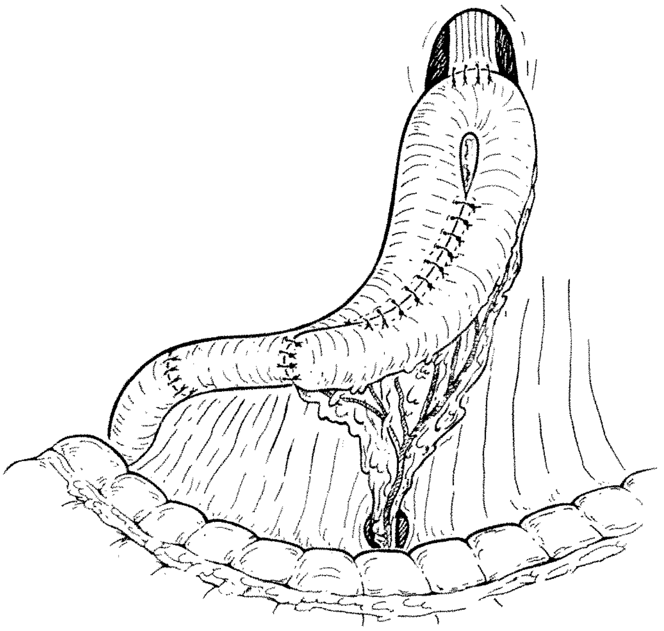

Figure 3 *The proximal end of pouch has been anastomosed to the oesophagus and the conduit to the duodenum. These anastomoses can be stapled*

Figure 4 *Operative photograph of the completed reconstruction demonstrating the isoperistaltic conduit from the reservoir to the duodenum. The pouch assumes a curved disposition not dissimilar from the normal stomach*

discharge and consisted of a small collection beneath the left diaphragm which drained spontaneously through the wound, with complete recovery. Chest infection occurred in ten patients (all smokers with chronic bronchitis) and wound infection occurred in four patients.

Survival

Thirteen patients (11 of the 17 having a relative curative operation, two of the 12 having an absolute curative operation) have died from disseminated disease within 3 years of surgery (median survival 1·4 years). None of these patients developed recurrence in the gastric bed or occlusion of the reservoir and its conduit by tumour. A further three patients died from benign disease (cerebrovascular accident, cardiac failure due to ischaemic heart disease and pneumonia after fracture of the femur). A post mortem was performed in two patients. In both cases the pouch appeared normal (*Figure 5*), had a capacity of 400 ml (undistended before fixation) and showed normal histology except for Paneth cell hyperplasia.

Nutritional outcome

Thirteen patients are alive 1–11 years after surgery (median 6 years). The assessment has been symptomatic and objective.

The symptomatic assessment is shown in *Table 2* using a scoring system of 0–3 for each symptom. The commonest ailment has been heartburn due to reflux of bile from the pouch into the lower oesophagus. This has been symptomatically controlled by sucralfate and has not led to any stricture formation, but persistent oesophagitis has been documented by endoscopy and biopsy in all five patients. Vomiting with food inspissation was encountered in one patient. This was caused by a stenosis of the distal anastomosis to the duodenum and required a secondary intervention 18 months after the operation. The objective assessment is outlined in *Table 3*.

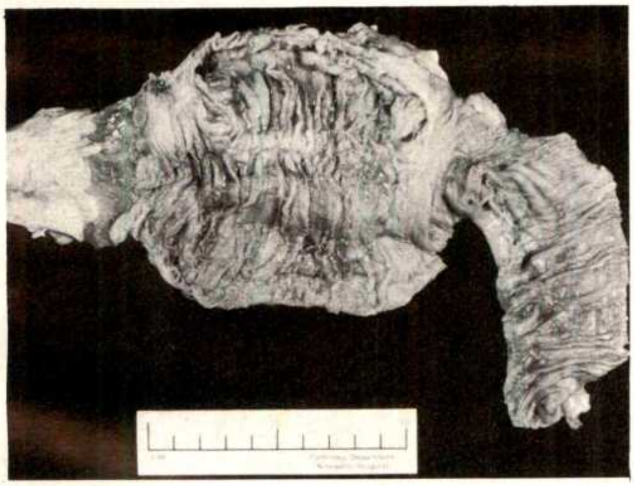

Figure 5 *Post-mortem appearance of the jejunal pouch 3 years after the operation*

Table 2 *Symptomatic assessment in 13 surviving patients*

	Score*			
Symptom	0	1	2	3
Dietary restriction	11	1	1	0
Early satiety	9	3	1†	0
Postprandial fullness	12	0	1†	0
Vomiting after meals	12	0	1†	0
Heartburn	8	3	1	1
Vasomotor dumping	13	0	0	0
Diarrhoea	11	2	0	0

* Score designation: 0, absence of complaint; 1, mild, no medication; 2, mild and frequent, moderate, requires medication; 3, severe and persistent; † patient who developed duodenal stenosis

Table 3 *Objective assessment of 13 surviving patients*

Mean haemoglobin level (g/dl)	13·1 (1·1)
Mean serum albumin level (g/dl)	37·0 (2·9)
Mean weight (kg)	64·0 (5·2)
No. of patients within 10% ideal weight	10
Endoscopy	
Normal	8
Grade 1–3 oesophagitis	5

Values in parentheses are s.d.

Discussion

Total gastrectomy is the treatment of choice for proximal gastric cancer as proximal gastrectomy does not achieve a satisfactory node clearance and is accompanied by severe oesophagitis. The incidence of cancer of the upper third of the stomach including cardia has increased worldwide at the expense of antral neoplasms[9,10]. Thus, apart from the ongoing controversy regarding the extent of resection and lymph node clearance, the absolute need for total gastrectomy has increased.

The nature of the optimum reconstruction after total gastrectomy for malignant disease remains unsettled and there have been no prospective clinical trials in this area. In the author's view, the type of reconstruction depends on the surgeon's assessment of the potential curability of the resection that has been performed. If the resection is considered palliative, then a simple reconstructive procedure such as a Roux-en-Y or loop jejunostomy with distal enteroenteric anastomosis is a sensible option. On the other hand when the resection is deemed to be potentially curative the surgeon should endeavour to reconstruct the upper gastrointestinal tract by a method that ensures a good functional and nutritional result, since long-term survival after successful curative surgery for gastric cancer must not be equated with long-term misery from significant postgastrectomy sequelae.

By virtue of its widespread general use, the Roux-en-Y procedure must be considered the standard reconstruction after total or subtotal gastrectomy. The main advantages of this procedure are ease of performance, safety and the diversion of bile from the proximal oesophagus provided the distal anastomosis is performed beyond 40 cm from the oesophageal anastomosis[14]. Nevertheless, this complication can still occur since the ultimate level and lie of the enteroenteric anastomosis in relation to the oesophageal anastomosis is determined by the extent and anatomy of the postoperative adhesions[15]. Thus, if the distal anastomosis adheres to the undersurface of the left hemidiaphragm, which is not infrequent when the spleen is removed, this results in a U loop of jejunum between the two anastomotic stomas encouraging both bile reflux and bacterial overgrowth.

The simple loop oesophagojejunostomy with distal enteroenteric anastomosis is generally regarded to be inferior to the Roux-en-Y reconstruction, although in practice the two procedures achieve the same functional results and there have not been any prospective clinical trials on the relative efficacy of these two forms of reconstruction. The loop jejunostomy is probably safer as the blood supply to the jejunal loop is less likely to be jeopardized.

Pouch reconstructions are used in patients after potentially curative resections. Some such as the Hunt–Lawrence pouch[16,17], the Tanner Roux-19[18], the Tolley[19] and the Lygidakis[20] procedures are based on the Roux-en-Y principle and thus entail duodenal bypass. Although anatomically sound, these procedures are unphysiological and can lead to bacterial overgrowth and steatorrhoea[21].

Others are constructed on the interposition principle and aim to restore duodenal continuity. These are based on jejunal interposition first reported by Henley as a primary reconstruction after gastrectomy[22] and subsequently used as a remedial operation for patients with severe postgastrectomy syndromes[23]. The same procedure was later reported by Longmire and Beal[24]. There is no doubt that jejunal interpositions are more physiological than the duodenal bypass procedures. In a well controlled experimental study in growing rats submitted to total gastrectomy, a significantly better growth rate and a shorter small bowel transit time were observed in the group reconstructed by a jejunal loop interposition than in the animals with a Roux-en-Y oesophagojejunostomy[25]. The early interposed jejunal pouches[26,27] had poor long-term results with the development of dilatation, stasis, ulceration and frank obstruction[28]. These complications were largely owing to the antiperistaltic nature of the conduit from the pouch to the duodenum. This consideration led to the design of the present pouch[11]. The long-term assessment of this pouch, which has an isoperistaltic exit channel, has been entirely favourable. The reconstruction is safe and leads to a satisfactory symptomatic and nutritional result. Prospective studies are now needed to compare its benefit in terms of quality of life and nutritional state with standard reconstructions such as the Roux-en-Y based procedures.

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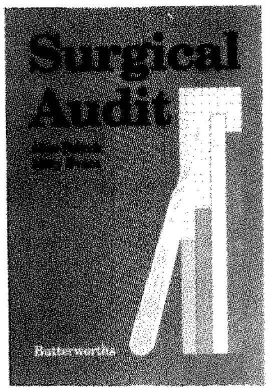

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Br. J. Surg. 1990, Vol. 77, April, 425–427

Continuous ^{99m}Tc-HIDA infusion as a method for measuring duodenogastric reflux

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The continuous ^{99m}Tc-HIDA infusion test is presented as a method for measuring duodenogastric reflux as well as for studying biliary elimination of the compound when it is administered by constant intravenous infusion. Thirty patients were studied: (a) ten patients with a T tube placed in the biliary tree were used to study the elimination of ^{99m}Tc-HIDA in the bile; (b) ten normal subjects were used as a control group; and (c) ten patients were studied who had undergone Billroth I gastrectomy for peptic ulceration. Studies of subjects in groups (b) and (c) were used to assess duodenogastric reflux by this test, correlating it with the measurement of bile acids in gastric juice. When ^{99m}Tc-HIDA was administered by constant intravenous infusion it resulted in an increased elimination in bile for the first 80–100 min, and the concentration in bile then remained relatively constant for the rest of the test. With respect to the duodenogastric reflux study group, reflux rates in the patients who had been operated on were higher than those in the control group, with statistically significant differences. Minimum reflux rates were found in the normal subjects. Assessment of reflux by ^{99m}Tc-HIDA correlated closely with the results of bile acid concentrations in Billroth I patients ($r = 0.75$, $P < 0.001$) and control subjects ($r = 0.85$, $P < 0.001$). Our results demonstrate that continuous ^{99m}Tc-HIDA perfusion is a useful, accurate and objective method for measuring duodenogastric reflux.

Keywords: Duodenogastric reflux, bile reflux gastritis, ^{99m}Tc-HIDA, bile acids and salts

Duodenogastric reflux has been implicated in the development of different pathological conditions such as peptic ulceration[1–3], various forms of gastritis in the intact stomach[4–6], postoperative gastritis and oesophagitis[7–12], and gastric stump cancer[13,14]. In medical practice it would be useful to have a method for quantifying this reflux since the degree of injury will depend (as it does with gastro-oesophageal reflux) on the number, intensity and duration of episodes of reflux.

This paper aims to present a new method for measuring duodenogastric reflux using a duodenal marker (^{99m}Tc-HIDA; ^{99m}Tc-Sn-2,6-diethylacetanilidoiminodiacetate) administered for 6 h by continuous intravenous infusion.

Patients and methods

Patients and volunteers

There were 30 patients and volunteers divided into two groups.

Group 1: patients with a T tube. This group consisted of ten patients, seven women and three men, with an average age of 53 years. A cholecystectomy plus choledochotomy had been performed, closing the bile duct over a T tube. The experiment was performed 10–12 days after the operation, once the patient had recovered and hepatic function tests had returned to normal.

Group 2: duodenogastric reflux study group. This group was divided into two subgroups: the control group (2a) consisted of ten normal subjects, eight men and two women, with no gastric, hepatic or biliary pathology and with an average age of 32 years. The hepatic function tests, liver and biliary ultrasonography, and gastroscopy were normal; the Billroth I group (2b) consisted of ten patients, seven men and three women, with an average age of 59 years. They had been operated on for type I gastric ulceration with antrectomy and reconstruction using a Billroth I technique.

Methods

Group 1. This group was used to determine the rate of ^{99m}Tc-HIDA elimination in bile when the radiopharmaceutical was administered for 6 h by constant intravenous infusion. Before beginning the test, six 100 ml solutions of physiological saline were prepared, each containing a progressively greater concentration of ^{99m}Tc-HIDA, as the half-life of this isotope is 6 h and its radioactivity decreases with time. These concentrations were calculated according to the radioactive disintegration formula:

$$N = N_0 \times e^{-\lambda t}$$

where N = concentration at time t; N_0 = initial concentration; λ = radioactive disintegration constant; and t = time.

The six solutions, to be infused during the first to sixth hours, contained 200, 224, 252, 286, 320 and 356 μCi, respectively.

At 08.00 hours, after a 12 h overnight fast, a peripheral vein was cannulated and infusion of the isotope was begun; bile was collected over the 6 h from the T tube by gentle syringe aspiration. The bile was collected in fractions at intervals of 20 min to determine the ^{99m}Tc-HIDA concentration in each sample. Similarly, blood was taken every 20 min to determine simultaneously the amount of radioactivity in the blood. A 1 ml sample was taken from each biological sample (bile and blood) to determine the concentration of the isotope. The activity of each sample was measured immediately in a γ spectrometer (Searle Analytic Incorporated, Illinois, USA; model 1185), activity being expressed in radioactive counts per minute (c.p.m.). Thus, the ^{99m}Tc-HIDA concentration in each sample was expressed as c.p.m. per ml.

Group 2. At 08.00 hours, after a 12 h overnight fast, a peripheral vein was cannulated and ^{99m}Tc-HIDA infusion was begun, the solution having been prepared as described above.

A Levin nasogastric tube was then introduced, and its position in the stomach was checked radiologically. During the first hour no gastric juice was aspirated for two reasons: first, the patient was allowed to settle and any nausea was given an opportunity to disappear; second, time was allowed for the isotope to be taken up by the liver, eliminated in the biliary tree, and passed to the duodenum. For the remaining 5 h gastric juice was constantly and gently aspirated by syringe suction. Sixteen samples of gastric juice were eventually obtained. The first sample corresponded to secretion during the first hour, and the other 15 to secretion over the remaining 5 h divided into 20-min intervals. From the samples of gastric juice obtained, 1 ml was used to determine

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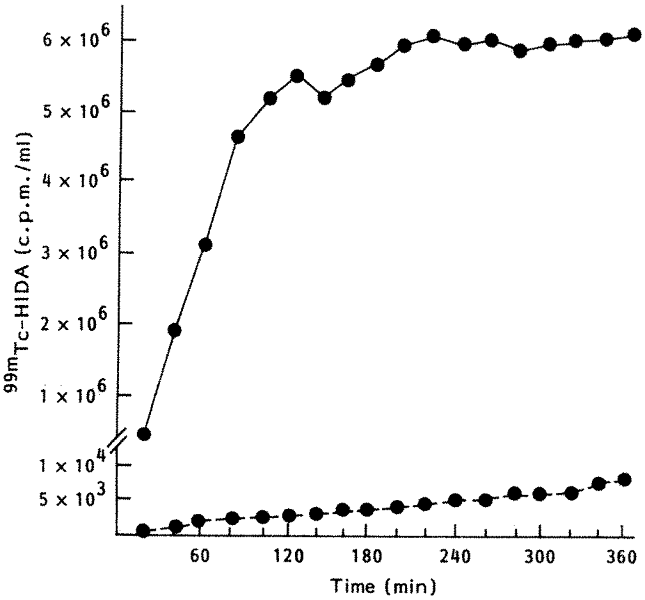

Figure 1 *Graph showing the biliary excretion (– – –) and blood elimination (——) of ^{99m}Tc-HIDA in ten patients with T tubes after choledochotomy*

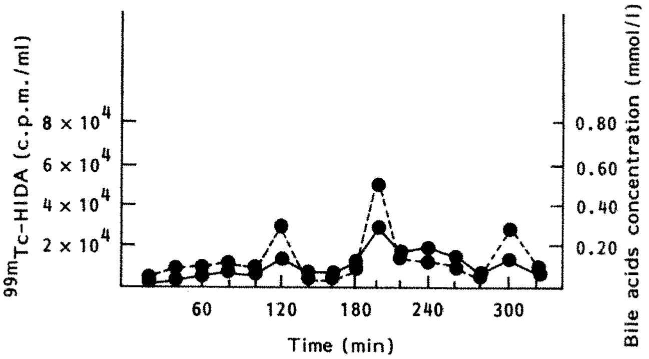

Figure 2 *Mean concentrations of ^{99m}Tc-HIDA (——) and bile acids (– – –) in gastric juice in control subjects*

the isotope concentration, and the rest was frozen at -20°C for subsequent determination of the concentration of total bile acids using the dehydrogenase–steroid method[15].

Statistical methods

The data were processed by a Honeywell Bull computer at the Data Processing Centre of the University of Murcia, and were subjected to the statistical program BMDP (BMDP Statistical Software, Los Angeles, California, USA). The relationship between ^{99m}Tc-HIDA and bile acid concentration was studied using a multiple regression analysis, calculating for each different situation the regression equation for bile acid concentration against ^{99m}Tc-HIDA concentration with time, with the 160 points corresponding to the 16 samples from the ten patients. Subsequently, the coefficient of partial correlation between the ^{99m}Tc-HIDA and bile acid concentration was calculated, eliminating the linear effect of time and subsequently evaluating its statistical significance.

Results

Pharmacokinetics of ^{99m}Tc-HIDA in blood and bile when administered by constant infusion

The ^{99m}Tc-HIDA concentration in bile and blood at each interval is shown in *Figure 1*. With regard to biliary concentrations, there were no statistically significant differences between the periods after the fifth 20 min interval, suggesting that the isotope concentration in bile increases for the first 80–100 min and then remains relatively constant.

Duodenogastric reflux study group

Control group. The mean concentrations of ^{99m}Tc-HIDA and bile acids in gastric juice at each interval are shown in *Figure 2*. The correlation between ^{99m}Tc-HIDA and bile acid concentrations was significant ($r=0{\cdot}85$, $P<0{\cdot}001$).

Billroth I group. The mean concentrations of ^{99m}Tc-HIDA and bile acids in gastric juice at each interval are shown in *Figure 3*. The correlation between ^{99m}Tc-HIDA and bile acid concentrations was highly significant ($r=0{\cdot}75$, $P<0{\cdot}001$).

Finally, duodenogastric reflux in patients who had undergone Billroth I gastrectomy was greater than in healthy volunteers (*Figure 4*), whether reflux was measured over the 5 h period by the ^{99m}Tc-HIDA method ($P<0{\cdot}001$) or by bile acid concentrations ($P<0{\cdot}001$).

Discussion

The pharmacokinetics of ^{99m}Tc-HIDA have been studied by Sorgi *et al.*[16] and Harding *et al.*[17]. After performing a choledochotomy they inserted a T tube into the patient's bile duct, injecting ^{99m}Tc-HIDA by intravenous bolus. At 30 min after the injection only 5 per cent of the administered dose was detected in the bloodstream. The peak of bile excretion occurred between 45 and 60 min after administration. After 2 h, 69 per cent of the administered dose had been eliminated by bile.

Our study of the pharmacokinetics of ^{99m}Tc-HIDA in bile and blood when administered by continuous intravenous infusion confirmed that ^{99m}Tc-HIDA is excreted rapidly in bile, leaving the blood with a low concentration (*Figure 1*). We also

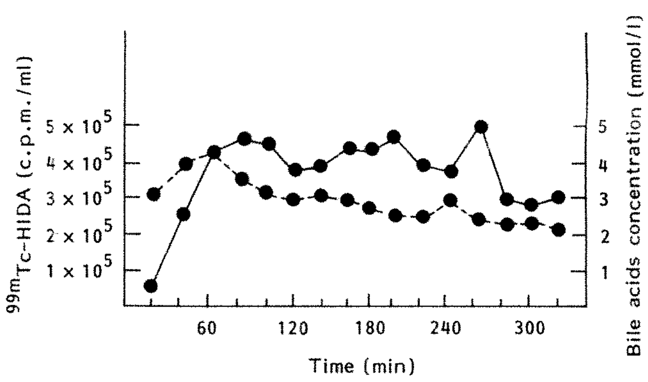

Figure 3 *Mean concentrations of ^{99m}Tc-HIDA (——) and bile acids (– – –) in gastric juice in patients who had undergone Billroth I gastrectomy*

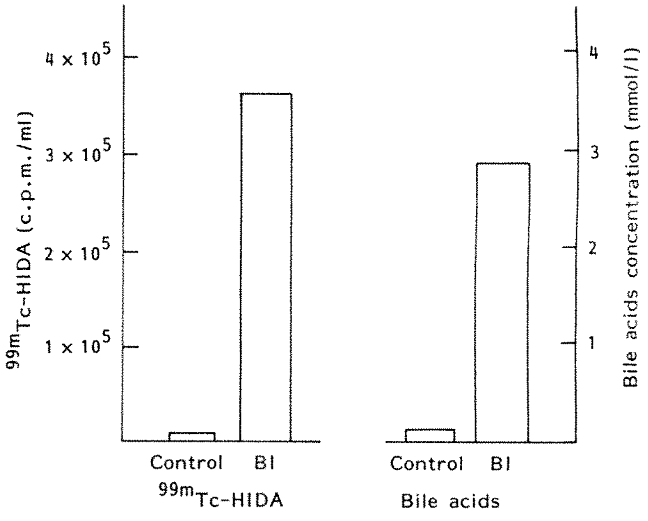

Figure 4 *Mean concentrations of ^{99m}Tc-HIDA and bile acids in gastric juice collected over 5 h in control subjects and patients who had undergone Billroth I gastrectomy (BI)*

observed that during the first 80–100 min the isotope concentration in bile increases, and then remains relatively constant for the duration of the infusion (*Figure 1*).

Some authors use an intravenous bolus injection of isotope to measure duodenogastric reflux[17–22], and so obtain a peak of maximum excretion 45–60 min after injection. Subsequently, bile concentration of the isotope drops gradually. With this method of injection, the concentration of the isotope in bile is not constant, a factor that can cause the test results to vary and, moreover, can limit study time. The time available for measuring reflux is important if reflux is to be assessed correctly, especially if it is to be quantified. Duodenogastric reflux is a frequent chance finding, and an isolated determination may give insufficient information about its real importance.

The time for which the isotope concentration remains constant is one of the main advantages of the present method over techniques such as those using duodenal markers administered by bolus intravenous injection. In 1982[23,24] we quantified reflux by intravenous bolus administration of bromsulphthalein and subsequent aspiration of gastric juice for 4 h at 15-min intervals. We found that in the first and fourth hours the concentration of bromsulphthalein in the duodenum was less than in the two intervening hours since its secretion in the bile was not continuous. This method enabled us to demonstrate that the amount of duodenogastric reflux in symptomatic patients who had had gastric surgery was greater than in asymptomatic patients who had undergone operation. Furthermore, if we used only the two intervening hours, the differences between both groups of patients were even greater, probably because the availability of the marker in the duodenum is greater during this period.

With continuous infusion of ^{99m}Tc-HIDA the problem of these differences has been solved. The method enables duodenogastric reflux to be measured reliably for as long as necessary, without the inconvenience of the marker causing fluctuating rates of bile excretion. Furthermore, the ^{99m}Tc-HIDA continuous infusion test is objective, with little margin of error and a high sensitivity, as it measures minimal episodes of reflux. A potential problem associated with the technique is irradiation of the patient. However, six infusions of 200–356 μCi ^{99m}Tc-HIDA administered with this technique, whereas in other scintigraphic explorations to determine reflux the patient receives 4–5 mCi ^{99m}Tc-HIDA. Thus, irradiation of the patient may be considered as quite low; moreover, ^{99m}Tc has a half-life of 6 h and is eliminated via the digestive tract.

To confirm the validity of our method, we simultaneously determined total bile acid concentration in gastric juice in each of the 16 samples in which ^{99m}Tc-HIDA concentration was determined. A highly significant correlation was found between ^{99m}Tc-HIDA and bile acid concentrations. Likewise, Houghton *et al.*[25] found a correlation between duodenogastric reflux determination using bile acid quantification and determination using ^{99m}Tc-HIDA injected as a bolus. This correlation was stronger when reflux rates were greater, perhaps because the marking capacity of reflux was greater. With regard to the quantity of reflux in the control and Billroth I groups, our findings agree with those of other authors[26–29] in that they reveal a higher reflux rate in the Billroth I group, as the mean concentrations of ^{99m}Tc-HIDA and bile acids were higher in the patients who had been operated on.

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428–431

Quantification of duodenogastric reflux in gastroduodenal peptic ulcer and in gastric operation patients, using a 24-h gastric pH measurement as a quantification technique

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Twenty-four-hour gastric pH measurement was used to study duodenogastric reflux. To differentiate between gastric hyposecretion and duodenogastric reflux, we also measured bile acid concentrations in the gastric juice, and regarded pH increases to above 4 as possible episodes of reflux. The procedure was used in 60 patients, divided into the following groups: (1) control group (ten patients); (2) duodenal ulcer (ten patients); (3) type 1 gastric ulcer (five patients); (4) type 3 gastric ulcer (five patients); (5) bilateral truncal vagotomy plus pyloroplasty (ten patients); (6) truncal vagotomy plus Billroth I partial gastrectomy (ten patients); and (7) truncal vagotomy plus Billroth II partial gastrectomy (ten patients). The amount of reflux (areas of pH >4) in the type 1 gastric ulcer and Billroth I and Billroth II groups was significantly greater than that found in the control, duodenal ulcer, type 3 gastric ulcer and truncal vagotomy plus pyloroplasty groups. The mean concentration of total bile acids was also greater in the gastrectomized patients than in the rest of the groups studied. In the type 1 gastric ulcer group the mean bile acid concentration was similar to that of the control group.

Keywords: Duodenogastric reflux, gastric pH measurement, gastric ulcer, duodenal ulcer, postoperative alkaline reflux gastritis

The pathological significance of duodenogastric reflux is not well known, and although it has been linked with the genesis of different pathological situations[1-13], progress in this area will be difficult while there is no adequate method to quantify reflux. Quantification has been attempted by various different approaches, including radiological[14-17] and endoscopic assessment[18,19], or the use of duodenal markers, either physiological[20-31], administered intraduodenally[32-36] or given intravenously[37-44]. The aim of the present study is to describe the use of 24-h continuous gastric pH measurement as a procedure to quantify duodenogastric reflux, utilizing the pH difference that usually exists between duodenum (pH 7) and stomach (pH 1–2). Gastric pH increases may be due to bile reflux but can also result from gastric hyposecretion. To avoid this source of error, pH measurement was associated with the determination of bile acid concentrations in the gastric aspirate at different times over the 24-h period.

Patients and methods

The procedure was applied to 60 patients, divided into the following groups:

1. A control group consisting of ten asymptomatic patients with normal upper gastrointestinal endoscopy
2. A duodenal ulcer group of ten patients with an endoscopic diagnosis of ulceration without stenosis
3. A type 1 gastric ulcer group of five patients in whom a chronic lesser curve peptic ulcer was seen at endoscopy at the level of the incisura angularis
4. A type 3 gastric ulcer group of five patients in whom chronic peptic ulcer in the prepyloric region was confirmed endoscopically
5. A vagotomy plus (Heineke–Mikulicz) pyloroplasty group consisting of ten patients
6. A group of ten patients who had undergone Billroth I partial gastrectomy with bilateral truncal vagotomy
7. A group of ten patients in whom a Billroth II partial gastrectomy with bilateral truncal vagotomy had been carried out.

Biliary ultrasonography was performed in all patients and recorded as normal. Patients who had undergone gastric surgery were asymptomatic, with the interval between operation and pH measurement ranging from 1 to 6 years.

We used a pHM 62 Standard pH meter with a GK 2801 stomach pH electrode (Radiometer A/S, Copenhagen, Denmark). The pH meter was connected to a 7754 B System recording polygraph (Hewlett-Packard, Palo Alto, California, USA), which incorporates thermosensitive paper with millimetre markings to record gastric pH continuously. To calculate the area of the pH trace where pH >4, we used a 9111 A digitalizer connected to a 9825T desktop computer (both Hewlett-Packard).

Patients were fasted overnight and at 09.00 hours, under fluoroscopic control, we passed the pH electrode into the stomach connected to a nasogastric probe (outer diameter 3·5 mm). Under fluoroscopic control we were able to prevent the electrode and/or nasogastric probe becoming coiled and were able to place them 5–7 cm from the pylorus or anastomotic aperture. The pH recording was then made uninterruptedly for 24 h. In accordance with Pandolfo *et al.*[45,46] we considered gastric pH increases to >pH 4 as possible reflux episodes. As pH >4 might be due to acid hyposecretion or to duodenogastric reflux, we also measured the concentration of bile acids in the gastric juice. Gastric juice was aspirated gently for a 5-min period at 2, 9 and 22 h respectively after recordings began. The samples of gastric juice were preserved at −20°C. Bile acid concentrations were determined by the dehydrogenase steroid method[47]. Thus we correlated the concentration of bile acids with the pH existing at the time of extraction.

The statistical parameters studied were means and standard deviations, and medians and ranges, both for reflux areas (pH >4) and bile acid concentrations.

The statistical study of the reflux areas (pH >4) was made using a one-way analysis of variance, for which the data were transformed

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Table 1 *Means, standard deviations, medians and ranges of the areas of pH >4 and of total bile acids in the different groups*

	Areas of pH >4		Bile acid concentrations	
Groups	Mean (s.d.)	Median (range)	Mean (s.d.)	Median (range)
Control	1·42 (1.82)	0·19 (0·0–4·80)	0·23 (0·34)	0·04 (0·0–1·0)
Duodenal ulcer	0·49 (0·53)	0·35 (0·0–1·87)	0·14 (0·35)	0·03 (0·0–1·9)
Type 1 gastric ulcer	14·25 (2·29)	15·36 (10·13–16·75)	0·17 (0·20)	0·07 (0·0–0·58)
Type 3 gastric ulcer	0·63 (0·49)	0·65 (0·0–1·50)	0·14 (0·19)	0·01 (0·0–0·6)
Vagotomy and pyloroplasty	6·38 (8·12)	3·78 (0·0–28·41)	0·57 (0·83)	0·25 (0·0–3·8)
Billroth I	19·50 (12·56)	18·61 (0·87–35·71)	1·41 (1·94)	0·60 (0·0–8·0)
Billroth II	17·14 (6·35)	17·53 (4·10–27·90)	1·67 (1·90)	1·00 (0·05–8·12)

s.d., Standard deviation

Table 2 *Reflux areas where pH >4. Statistical comparison of means applying ln(0·5+area) in the different groups*

	Control	DU	GU1	GU3	V+P	BI+BTV	BII+BTV
Control	–	n.s.	$P<0{\cdot}005$	n.s.	n.s.	$P<0{\cdot}001$	$P<0{\cdot}001$
DU		–	$P<0{\cdot}001$	n.s.	n.s.	$P<0{\cdot}001$	$P<0{\cdot}001$
GU1			–	$P<0{\cdot}005$	$P<0{\cdot}005$	n.s.	n.s.
GU3				–	n.s.	$P<0{\cdot}001$	$P<0{\cdot}001$
V+P					–	$P<0{\cdot}001$	$P<0{\cdot}005$
BI+BTV						–	n.s.
BII+BTV							–

DU, duodenal ulcer; GU1, type 1 gastric ulcer; GU3, type 3 gastric ulcer; V + P, vagotomy and pyloroplasty; BI + BTV, Billroth I and bilateral truncal vagotomy; BII + BTV, Billroth II and bilateral truncal vagotomy; n.s., not significant

Table 3 *Statistical comparison of means of bile acid concentrations in the different groups after applying a two-way analysis of variance*

	Control	DU	GU1	GU3	V+P	BI+BTV	BII+BTV
Control	–	n.s.	n.s.	n.s.	n.s.	$P<0{\cdot}001$	$P<0{\cdot}001$
DU		–	n.s.	n.s.	n.s.	$P<0{\cdot}001$	$P<0{\cdot}001$
GU1			–	n.s.	n.s.	$P<0{\cdot}005$	$P<0{\cdot}001$
GU3				–	n.s.	$P<0{\cdot}005$	$P<0{\cdot}001$
V+P					–	$P<0{\cdot}002$	$P<0{\cdot}001$
BI+BTV						–	n.s.
BII+BTV							–

DU, duodenal ulcer; GU1, type 1 gastric ulcer; GU3, type 3 gastric ulcer; V + P, vagotomy and pyloroplasty; BI + BTV, Billroth I and bilateral truncal vagotomy; BII + BTV, Billroth II and bilateral truncal vagotomy; n.s., not significant

logarithmically ($y=\ln(0{\cdot}5+\text{area})$). For bile acid concentrations, we used a two-way analysis of variance of random effects. Both analyses were completed with comparisons between pairs of means using means equality contrasts.

We studied the possible relationship between pH and bile acid concentrations in each group using linear regression analysis and obtaining the equations of the regression curves and the coefficient of correlation[48].

Results

Areas of pH >4

These were significantly larger in the type 1 gastric ulcer group and Billroth I and Billroth II groups than in the control, duodenal ulcer, type 3 gastric ulcer and vagotomy plus pyloroplasty groups (*Tables 1* and *2*).

With the gastric surgery groups the patients who had undergone vagotomy plus pyloroplasty had smaller areas of pH >4 than the Billroth I and Billroth II patients ($P<0{\cdot}005$) (*Table 2*). There were no statistically significant differences between the Billroth I and Billroth II groups (*Table 2*).

Determination of bile acid concentration

The overall mean of total bile acid concentration in the gastric resection patients was much higher than that found in the remaining groups studied (*Table 1*), with no statistically significant differences being found between the Billroth I and Billroth II groups (*Table 3*).

The mean of total bile acid concentrations in non-operated patients was lower than that found in the patients with vagotomy plus pyloroplasty, although the differences were not statistically significant (*Tables 1* and *3*).

Statistical correlations between pH and bile acid concentration in each of the groups

As can be seen in *Table 4*, gastric pH was significantly correlated with bile acid concentration in the control, duodenal ulcer, vagotomy plus pyloroplasty and Billroth I gastrectomy groups. However, there was no correlation in the type 1 gastric ulcer, type 3 gastric ulcer, and Billroth II gastrectomy groups.

Table 4 *Correlation between pH at the time of gastric juice extraction and bile acid concentration*

Group	Regression equation	r	$100r^2$ (%)	$P<$
Control	$y=-0{\cdot}097+22x$	0·46	20·25	0·05
Duodenal ulcer	$y=-0{\cdot}31+0{\cdot}28x$	0·89	79·21	0·001
Type 1 gastric ulcer	$y=0{\cdot}20-0{\cdot}0x$	−0·05	0·16	n.s.
Type 3 gastric ulcer	$y=0{\cdot}067+0{\cdot}05x$	0·08	0·49	n.s.
Vagotomy and pyloroplasty	$y=-0{\cdot}18+0{\cdot}05x$	0·61	37·21	0·01
Billroth I	$y=-1{\cdot}09+0{\cdot}47x$	0·49	23·04	0·05
Billroth II	$y=-0{\cdot}23+0{\cdot}32x$	0·21	0·41	n.s.

y, Concentration of bile acids; $x=$pH; r, coefficient of regression between x and y; 100 r^2, percentage of pH that depends on bile acids; n.s., not significant

Discussion

Knowing whether duodenogastric reflux exists at any particular time is of little interest pathologically, as the stomach has efficient mechanisms to deal with such reflux, notably gastric secretion in response to gastrin and antral motor activity which sweeps this reflux material towards the duodenum[49,50].

Twenty-four-hour gastric pH measurement is open to error in interpretation, as pH increases could be connected with gastric hyposecretion and not with bile reflux. To obviate this drawback, we obtained gastric juice on three occasions over a 24-h period and determined total bile acid concentrations in the samples, correlating them with the pH existing at that time. Thus, if variations in gastric pH are correlated with variations in bile acid concentration in the gastric juice, they must be attributed to reflux episodes. If they are independent, they must be connected with gastric hyposecretion.

Another factor that could affect the results is the periodical emptying of the gallbladder into the duodenum, which means that any increase in pH above 4 may be secondary to the reflux of duodenal and pancreatic juice into the stomach. This problem is also shared by the methods that are based on determining gastric juice concentrations of substances eliminated by the bile such as bile acids, bromsulphthalein and ^{99m}Tc-Sn-2,6-diethylacetanilidoiminodiacetate.

As occurs with gastro-oesophageal reflux, duodenogastric reflux may be found in healthy subjects without there being any pathological significance[8,51–53]. In our series, in the control group, the mean of areas of pH >4 and the concentration of bile acids are very low. Of the ten patients studied only one showed reflux episodes, especially at night, which were of short duration and weak intensity.

In the duodenal ulcer group, some authors[10,54–59] report a high level of duodenogastric reflux. Others, however[5,8,60], found no differences between the quantity of reflux in duodenal ulcer patients and normal subjects. In our series, there was no statistically significant difference between duodenal ulcer patients and normal subjects.

In the type 1 gastric ulcer group, several authors[5–7,14,60] report high reflux readings. However, other authors[34,52,61] did not find high levels of reflux in this type of gastric ulcer. Our results show significantly larger areas of pH >4 than those of the control group. The mean concentration of bile acids in gastric juice, however, was very low and similar to that of the control group, with no statistically significant correlation between pH readings and bile acid levels. This means that the hypoacidity that exists in the stomach of patients with type 1 gastric ulcer is connected with hyposecretion and not with duodenogastric reflux, as was reported by Johnson[62].

With regard to the type 3 gastric ulcer group, our results agree with those of Schumpelick and colleagues[63] in that no statistically significant differences were found between these patients and the control group for any of the parameters studied.

Finally, with gastric surgery patients our results are consistent with those obtained by other authors[64–69] in that they demonstrate a reflux rate that is significantly higher than that of the normal subjects. When comparing the different surgery groups we noted that gastric resection associated with bilateral truncal vagotomy induces more reflux than pyloroplasty associated with vagotomy. On the other hand, our results show that the type of reconstruction used after gastric resection (gastroduodenostomy or gastrojejunostomy) does not significantly modify the rate of duodenogastric reflux.

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Endoscopic and radiological appraisal of gastric varices*

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Of 104 patients with portal hypertension who were subjected to oesophageal variceal sclerotherapy, gastric varices were seen in 81 (78 per cent) at endoscopy and 69 (74 per cent) at splenoportography. In 50 (48 per cent) patients gastric varices were seen at the initial endoscopic examination and in 31 they developed during follow-up at intervals varying from 1 to 56 weeks. Gastric varices were seen significantly more often along the lesser curvature than in the gastric fundus and the left gastric vein was the main feeding vessel in 75 per cent of cases. Varices bled in nine of 81 patients and bleeding was seen significantly more often from fundal varices (30 per cent) than from lesser curve varices (5 per cent) ($P<0\cdot02$). The incidence of gastric varices is high, and contrary to popular belief they are more often located along the lesser curvature of the stomach than in the gastric fundus.

Keywords: Splenoportography, gastric varices

Endoscopic variceal sclerotherapy appears to have solved the problem of oesophageal varices to a great extent. However, gastric varices remain an enigma for most clinicians. The incidence of the latter is not well documented. While some feel that oesophageal varices are nearly always accompanied by gastric varices[1,2], others have reported only a 6–34 per cent association with gastric varices[3–5]. Few sclerotherapists mention the impact of variceal sclerotherapy on the subsequent development of gastric varices and little is known about the anatomical location and the feeding veins of gastric varices. This prospective study was done to determine the endoscopic and radiological incidences and the anatomical location of gastric varices at the beginning of sclerotherapy and during subsequent follow-up, and to determine the incidence of bleeding from such varices.

Patients and methods

From February 1985 to March 1987, 104 patients, with portal hypertension and at least one documented bleed from oesophageal varices, were included in the study. The aetiology of portal hypertension was established by liver biopsy and portovenography.

At endoscopy oesophageal varices were graded from 1 to 4 (Reference 6). The presence or absence and the location of gastric varices were recorded. If the oesophageal variceal columns were continuous with gastric variceal columns, this was noted. Oesophageal variceal sclerotherapy was then performed with 3 per cent aqueous phenol using a freehand intravariceal injection technique (S. K. Mathur *et al.*, unpublished results). Repeat sclerotherapy was done at intervals of 3 days for the first three sessions and subsequently at monthly intervals. The persistence or disappearance of the gastric varices was recorded at each subsequent endoscopic examination.

Gastric varices present at initial endoscopy were termed primary, and those which appeared subsequently during the course of sclerotherapy and follow-up were termed secondary. The interval between first sclerotherapy and appearance of secondary gastric varices was recorded, as was the number of sclerotherapy sessions before the development of secondary lesions.

Gastric varices and their feeding vessels were also shown radiologically using splenoportography[7] before subjecting patients to sclerotherapy. The splenoportograms were evaluated for the presence or absence of gastric varices, and their location was recorded (along lesser curve or fundus of the stomach or both). The feeding vessels to the gastric varices were noted and labelled as: (1) short gastric veins (from spleen to fundus of stomach); (2) left gastric vein (from splenic vein to lesser curvature of the stomach); and (3) retrogastric veins (from splenic vein and multiple unnamed retroperitoneal collaterals to gastro-oesophageal junction). The endoscopist and radiologist recorded their findings individually and were not aware of each other's findings until the final analysis of results.

Statistical analysis was done using the χ^2 test with Yates' correction, if appropriate, and Fisher's exact probability test.

Results

Seventy males and 34 females had endoscopic oesophageal variceal sclerotherapy. Ages ranged from 2 to 70 years with a mean (s.d.) of 28 (17) years. The cause of portal hypertension was cirrhosis in 44 patients, extrahepatic portal vein obstruction in 55 and non-cirrhotic portal fibrosis in five.

Endoscopic incidence of gastric varices

Primary gastric varices were seen at initial endoscopy in 50 (48 per cent) patients. The incidence of primary gastric varices was 30 of 55 (55 per cent) in extrahepatic portal vein obstruction, 18 of 44 (41 per cent) in cirrhosis, and two of 5 (40 per cent) in non-cirrhotic portal fibrosis. Differences between the three groups were not statistically significant.

Of the remaining 54 patients who did not have gastric varices at initial endoscopy, 31 developed secondary gastric varices at a mean(s.d.) interval of 6·6 (0·7) weeks (range 1–56 weeks) after starting sclerotherapy. These secondary gastric varices were noted after a mean(s.d.) of 2·1 (1·9) sclerotherapy sessions (range 1–8 sessions). The incidence of secondary gastric varices did not depend on the aetiology of portal hypertension, being 16 of 26 (62 per cent) in cirrhosis, 13 of 25 (52 per cent) in extrahepatic portal venous obstruction, and two of three (67 per cent) in non-cirrhotic portal fibrosis. Both primary and secondary gastric varices were more often associated with grade 3 and grade 4 oesophageal varices than with grade 1 and grade 2 (*Table 1*) and both persisted during follow-up, both before and after the obliteration of oesophageal varices.

Anatomical location of gastric varices

At endoscopy, primary and secondary gastric varices were respectively present along the lesser curve of the stomach in 37 of 50 (74 per cent) and 23 of 31 (74 per cent) patients, along the gastric fundus and lesser curve in nine (18 per cent) and seven (23 per cent), and along the fundus in four (8 per cent) and one (3 per cent) patients. Thus the overall incidence of lesser curve gastric varices was 60 out of 81 patients (74 per cent) which was significantly higher than that of isolated fundal

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Table 1 *Endoscopic incidence of gastric varices related to grade of oesophageal varices*

Grade of oesophageal varices	Primary GV/ oesophageal varices*	Secondary GV/ oesophageal varices†	All GV/ oesophageal varices‡
1	4/10 (40)	1/6(16)	5/10 (50)
2	7/24 (29)	8/17(47)	15/24 (62)
3	34/58 (58)	16/24(66)	50/58 (86)
4	5/12 (41)	6/7(85)	11/12 (91)

Values in parentheses are percentages; GV, gastric varices. * $P<0{\cdot}05$ (grade 3 *versus* grade 2); † $P<0{\cdot}02$ (grade 4 *versus* grade 1); ‡ $P<0{\cdot}02$ (grade 3 *versus* grade 1), $P<0{\cdot}05$ (grade 3 *versus* grade 2) and $P<0{\cdot}05$ (grade 4 *versus* grade 1)

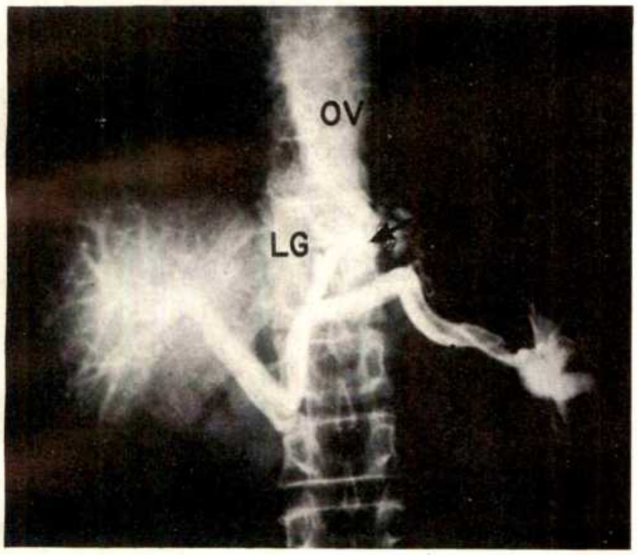

Figure 1 *Splenoportogram showing left gastric vein (LG) forming lesser curve varices (arrow) continuous with oesophageal varices (OV)*

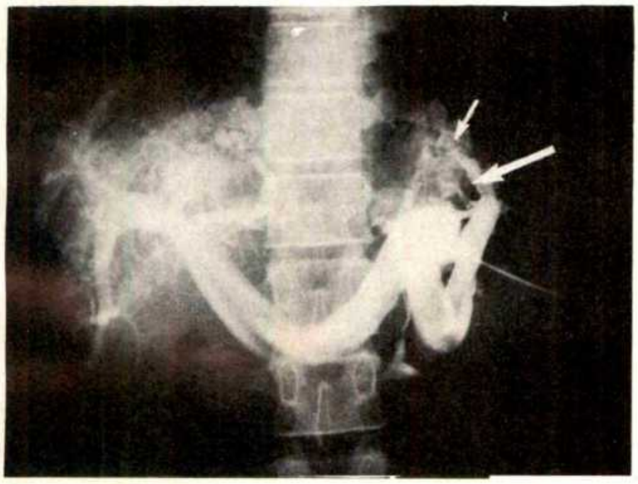

Figure 2 *Splenoportogram showing short gastric veins (large arrow) forming the fundial varices (small arrow)*

varices (five of 81) and of a combination of fundal and lesser curve varices (16 of 81) ($P<0{\cdot}01$). The lesser curve gastric varices were continuous with oesophageal varices in all cases of primary gastric varices and in those patients in whom secondary varices developed before obliteration of oesophageal varices. The location of gastric varices was independent of the aetiology of portal hypertension.

Radiological incidence of gastric varices

Of 104 splenoportograms, 93 were evaluated and 11 were unsatisfactory. Gastric varices were seen in 69 of 93 (74 per cent) patients. The radiological incidence of gastric varices was 41 of 55 (75 per cent) in extrahepatic portal vein obstruction, 24 of 34 (71 per cent) in cirrhosis and four of four (100 per cent) in non-cirrhotic portal fibrosis.

Anatomical location of gastric varices and feeding vessels

Gastric varices were seen along the lesser curvature of the stomach in 52 of 69 (75 per cent) patients (*Figure 1*) and along the fundus in six (9 per cent) patients (*Figure 2*) ($P<0{\cdot}01$). In 11 (16 per cent), gastric varices were located along both the lesser curve and fundus of the stomach (*Figure 3*). The location of gastric varices was independent of the aetiology of portal hypertension.

In 69 patients in whom gastric varices were recognized by splenoportography, the main feeding vein was the left gastric in 75 per cent (*Figures 4* and *5*) and the short gastric veins in 25 per cent (*Figures 2* and *3*). Details of feeding vessels are shown in *Table 2*.

Correlation between endoscopic and splenoportogram findings

In 93 patients who had undergone endoscopy as well as splenoportography, both investigations showed the presence of

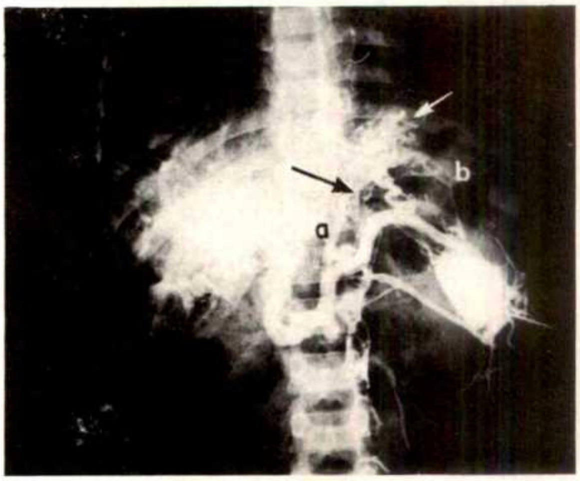

Figure 3 *Splenoportogram showing left gastric vein (a) and short gastric veins (b) forming gastric varices along the lesser curve (black arrow) and gastric fundus (white arrow)*

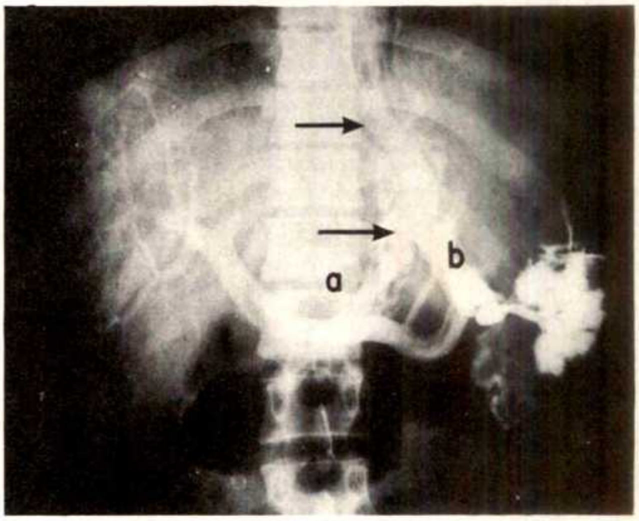

Figure 4 *Splenoportogram showing left gastric vein (a) and retrogastric veins (b) feeding lesser curve gastric varices (bottom arrow) and oesophageal varices (top arrow)*

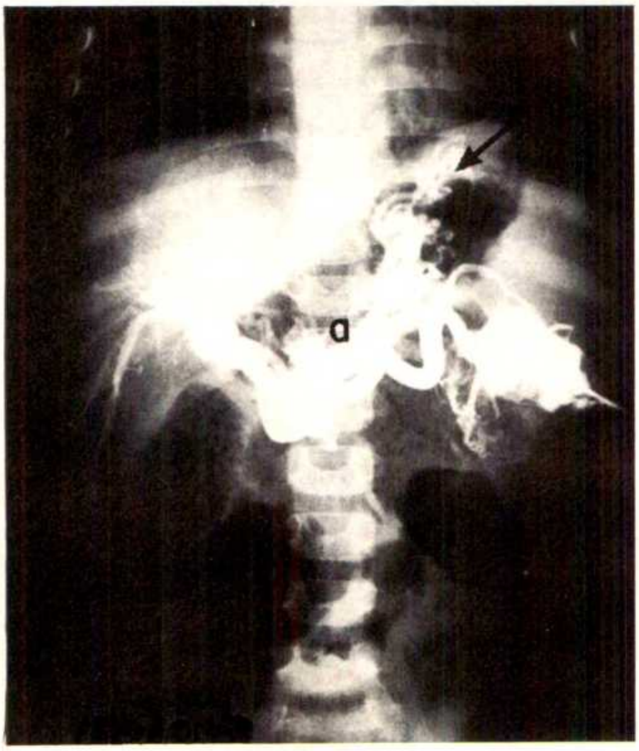

Figure 5 *Splenoportogram showing left gastric vein (a) feeding fundal varices (arrow)*

Table 2 *Veins feeding gastric varices according to splenoportogram, related to aetiology of portal hypertension*

Feeding vein	EHVO ($n=55$)	Cirrhosis ($n=34$)	NCPF ($n=4$)	Total ($n=93$)
Left gastric	24	11	3	38
Left gastric and retrogastric	6	8	0	14
Left gastric and short gastric	7	3	1	11
Short gastric	3	1	0	4
Short gastric and retrogastric	1	1	0	2
Total	41	24	4	69

EHVO, extrahepatic portal venous obstruction; NCPF, non-cirrhotic portal fibrosis

gastric varices in 68 patients and their absence in 13 patients. The overall correlation between endoscopic and radiological findings was 81 out of 93 (87 per cent) patients (*Table 3*). There was no statistically significant difference in the incidence of lesser curve varices as seen at endoscopy (73 per cent) and splenoportography (75 per cent). The endoscopic finding of lesser curve varices in continuity with oesophageal varices was confirmed by splenoportography

Incidence of bleeding from gastric varices

Gastric varices bled in five of 50 (10 per cent) patients with primary varices and four of 31 (13 per cent) with secondary varices. Bleeding was seen more often from fundal varices (six of nine) than from lesser curve varices (*Table 4*). Out of 21 cases of fundal varices, bleeding was seen in six compared with only three out of 60 cases with lesser curve varices ($P<0\cdot02$). Bleeding from gastric varices was noticed after the obliteration of oesophageal varices, at a mean(s.d.) interval of 8·3 (3·0) weeks (range 1–32 weeks).

Discussion

Although the prevalence of gastric varices is unknown, they are said to be uncommon[3]. The present findings are contrary to this belief, however, as the gastric varices were detected in 78 per cent of patients. A similarly high incidence of gastric varices has been reported by Paquet (60–70 per cent)[8] and Clark *et al.* (100 per cent)[1], but others have reported incidences of only 6–34 per cent[3–5]. The wide discrepancy between present data and those of others may be because all other series are retrospective analyses of patients who underwent oesophageal variceal sclerotherapy and in whom no extra attempt might have been made to document gastric varices.

The impact of oesophageal variceal sclerotherapy on gastric varices is not clearly known. Hosking and Johnson[3] have reported development of gastric varices in 21 of 208 patients during long term follow-up. In the present series 57 per cent of patients who did not have gastric varices at initial endoscopy developed gastric varices during or after completion of oesophageal variceal sclerotherapy. There was no correlation between the development of secondary gastric varices and the time interval and number of sclerotherapy sessions. These findings are similar to other reports[3]. No change in the appearance of primary and secondary gastric varices was noticed during oesophageal variceal sclerotherapy or after the obliteration of varices. MacDougal *et al.*[9] have also reported persistence of gastric varices after disappearance of oesophageal varices, contrary to Terblanche *et al.*[10] and Sarin *et al.*[4] who have reported the disappearance of gastric varices after the sclerosis of distal oesophageal veins. The mechanism of disappearance of gastric varices is thought by these workers to be due to retrograde flow of sclerosant from oesophageal to gastric varices.

Splenoportography has been used as a diagnostic technique to demonstrate gastro-oesophageal varices[11]. Hahn-Pedersen *et al.*[12] reported splenoportographic evidence of gastric varices in 31 of 57 patients. Others have reported a 100 per cent incidence of gastric varices on splenoportography[13]. In the present series splenoportography revealed the presence of gastric varices in 74 per cent of patients. Discrepancy between endoscopic and radiological incidence of gastric varices has been reported. Muhletaler *et al.*[14] found gastric varices at endoscopy in only four of ten patients diagnosed as having gastric varices

Table 3 *Location of gastric varices: correlation between endoscopic and splenoportogram findings in 93 patients having both investigations*

	Endoscopy			
	Lesser curve	Lesser curve and fundus	Fundus	None
Splenoportogram				
Lesser curve	52	—	—	—
Lesser curve and fundus	—	11	—	—
Fundus	—	—	5	1
None	6	5	—	13

Table 4 *Incidence of bleeding from gastric varices*

	Primary varices ($n=50$)	Aecondary varices ($n=31$)	Total ($n=81$)
Extrahepatic portal vein obstruction	2*/30	2*/13	4/43
Cirrhosis	3/18	2*/16	5/34
Non-cirrhotic portal fibrosis	0/2	0/2	0/4
Total	5 (10)	4 (13)	9 (11)

Values in parentheses are percentages; * bleeding from fundal varices on splenoportography. In the present study, splenoportography and endoscopic findings regarding presence or absence of gastric varices correlated well in 87 per cent of cases.

Gastric varices have been described as ones which pass through cardia and line the fundus in a worm-like fashion[2]. Despite this, gastric varices in this study were seen significantly more often along the lesser curvature of the stomach than in the gastric fundus. Most of the previous reports about gastric varices have failed to mention their location within the stomach[10,15]. In the present series, the presence of longitudinal columns along the lesser curvature of the stomach was documented as lesser curve gastric varices, because in normal subjects and in patients with portal hypertension without gastric varices the lesser curve mucosa is almost bald, without longitudinal folds. These lesser curve variceal columns were found to be continuous with the oesophageal variceal columns. However, unlike oesophageal varices these gastric varices did not appear bluish, whereas fundal varices were seen as bluish bunches rather than longitudinal columns.

Takashi *et al.*[16] have demonstrated the continuation of the left gastric vein as gastro-oesophageal varices by performing left gastric venography. Our splenoportographic findings have also shown that in majority of the cases the feeding vessel to the gastric varices was the left gastric vein, along with retrogastric veins, rather than short gastric veins. Karr and Wohl[17] have also reported less frequent involvement of short gastric veins.

The incidence of bleeding from gastric varices was low (11 per cent) in this series and there was no significant difference in incidence of bleeding between primary and secondary lesions. However the incidence of bleeding from fundal varices was higher than from lesser curve varices. Others have reported bleeding from gastric varices in 3–30 per cent of cases[1,4,5,15,18–20].

Until now no precise classification has been described for gastric varices, although Hosking and Johnson[3] have divided them into type 1 (those which appear as inferior extensions of oesophageal varices across the squamocolumnar junction), type 2 (located in the fundus and nearly always accompanied by oesophageal varices) and type 3 (located in the fundus in the absence of oesophageal varices). We have classified gastric varices according to their anatomical location in the stomach: (1) lesser curve varices which are often continuous with oesophageal varices; (2) fundal varices located in the fundus irrespective of aetiology of portal hypertension and which are similar to types 2 and 3 of Hosking and Johnson's classification; and (3) combination of fundal and lesser curve varices which perhaps could be labelled as type 4 gastric varices. This classification could help in rationalizing the therapy for gastric varices. Lesser curve varices (type 1) can be treated by sclerotherapy[3]. Fundal varices respond poorly to sclerotherapy[15,21] and require some form of surgical procedure[3,15]. The combination of fundal and lesser curve varices could be managed according to the site of bleeding. In order to study the impact of oesophageal variceal sclerotherapy on the development of gastric varices, we also propose that they should be classified as: (1) primary (those present before starting oesophageal sclerotherapy), and (2) secondary (those developing during and subsequent to sclerotherapy).

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Prognostic significance of serosal invasion and free intraperitoneal cancer cells in gastric cancer

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Survival rates after curative gastrectomy for advanced gastric cancer among 238 patients in whom the cancer was invading the serosa were compared with 283 patients without serosal invasion. Generalized Wilcoxon estimates for 5-year survival rate were 47·1 per cent for patients exhibiting serosal invasion and 75·9 per cent for patients without serosal invasion. The frequency of lymph node metastasis increased proportionately with the extent of serosal invasion: 18·4 per cent in cases of S_0; 53·8 per cent in cases of S_1; 80·0 per cent in cases of S_2; and 91·4 per cent in cases of S_3. The higher the aggregate total of S (serosal invasion) and n (lymph node metastasis) factors, the lower the 5-year survival rate. In addition, patients with serosal invasion had a propensity for peritoneal dissemination of cancer cells; the percentage of cases with intraperitoneal free cancer cells increased with the extent of serosal invasion. It is worth noting that when cancer infiltration proceeded to the deeper layers and was accompanied by nodal metastasis, cancerous invasion of the perinodal fatty tissue was frequently evident. Therefore, unfavourable prognosis after curative resection in gastric cancer patients with serosal invasion may be largely dependent on whether or not the cancer has invaded the peritoneal cavity and the perinodal fatty tissue.

Keywords: Gastric cancer, serosal invasion, free intraperitoneal cancer cell

The 5-year survival rate for gastric cancer diagnosed at an early stage in Japan is over 90 per cent, compared with 30–40 per cent for cases discovered in advanced stages[1,2]. In the last few years, the 5-year survival rate following gastrectomy for gastric cancer has increased rapidly in Japan. This can be attributed both to the improved curative effect of gastrectomy itself and to the increasingly early diagnosis of cases, the latter being the more important factor.

Many variables are considered to be important in the prognosis of patients with stomach cancer. Maruyama[3] analysed 25 variables in gastric cancer patients by multivariate analysis and identified the following five factors as especially important: depth of invasion, lymph node metastasis, cancer type, location and histological character. Of 11 variables investigated by Curtis *et al.*[4] in 4785 gastric cancer patients, depth of invasion, lymph node metastasis, and distant metastasis were the three most significant. In another study using multivariate analysis, Nakazato *et al.*[5] reported that the most important prognostic factors in cases of gastric cancer were distant metastasis, serosal involvement and lymph node metastasis.

After almost all non-curative gastrectomies and some curative ones, gastric cancer recurs. Most of the statistics concerning death due to cancer recurrence after gastrectomy[6] indicate that over half of the patients show peritoneal dissemination followed in order of importance by distant metastasis via lymphatic and/or haematogenous spread, and reappearance of the cancer at anastomotic stomata.

To clarify the reasons for poor prognoses in cases of gastric cancer with serosal invasion after curative resection, we analysed the prognostic variables associated with gastric cancer, with special reference to the relationship between serosal invasion and both the pattern of lymph node metastasis and presence of free cancer cells in the peritoneal cavity.

Patients and methods

A total of 1035 patients registered at the Kansai Medical University with clinical and histological diagnoses of gastric cancer between 1975 and 1986 were reviewed. Data already recorded by the Registry from patient notes included clinical features, diagnostic methods, treatment, histological findings and survival data. Of the 1035 patients, 820 patients (79·2 per cent) underwent gastrectomy. The number of curative gastrectomy cases was 521 (curative rate 63·5 per cent). The group comprised 319 men and 202 women, of ages ranging from 25 to 86 years (mean 58·3 years). All had primary adenocarcinoma of the stomach. Operative findings were assessed and described according to the criteria described in 'General Rules for Gastric Cancer Study in Surgery and Pathology' compiled by the Japanese Research Society for Gastric Cancer[7]. According to the criteria, serosal invasion was classified based on gross findings as follows: S_0, no serosal invasion; S_1, suspected serosal invasion; S_2, defined serosal invasion; and S_3, invasion of contiguous structures. Peritoneal metastasis was classified on gross findings as follows: P_0, no peritoneal dissemination; and P(+), macroscopically evident peritoneal dissemination. Resected tissues were examined to determine the depth, mode and histological type of cancer invasion, and whether or not metastasis of the lymph nodes had occurred. Cancers whose invasion of the gastric wall was no deeper than the subserosal layer were included in the category of ps (−) cancers (negative serosal invasion). Any cancer whose invasion was present on a serosal surface exposed to the peritoneal cavity was classified as ps(+). Histological findings of lymph node metastasis were classified as follows: n_0, no lymph node metastasis; n_1, nodal metastasis surrounding the stomach; n_2, nodal metastasis along the main arteries including the coeliac axis. The histological type was determined according to a report by the Japanese Research Society Committee on Histological Classification of Gastric Cancer[7]. The spread of cancer cells into and around the regional lymph nodes was classified according to our criteria: type I, cancer cells were confined within the marginal sinus; type II, cancer cells infiltrated the medullary sinus; type III, cancer cells spread throughout the entire lymph node system; and type IV, cancer cells emerged into the perinodal adipose tissue beyond the lymph nodes.

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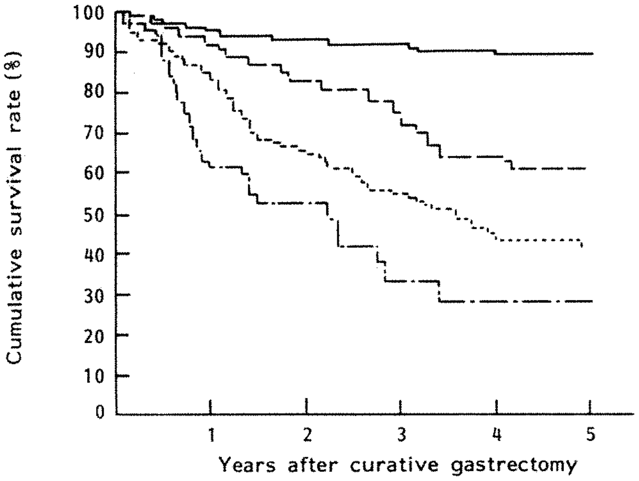


——— 283	205	155	120	100	81
— — — 78	55	36	27	20	18
.... 125	91	64	46	32	20
—·— 35	20	16	7	4	4

Figure 1 *Cumulative survival rates in cases of curative gastrectomy related to macroscopic serosal invasion (total number of patients = 521); —— S_0, no serosal invasion (283); --- S_1, suspected serosal invasion (78); ----- S_2, definite serosal invasion (125); -·-·- S_3, invasion of contiguous structures (35);* $P<0.01$. *Number of patients eligible for analysis at each time point are shown*

For statistical evaluation the χ^2 test was used, and for survival analysis the generalized Wilcoxon estimate was used.

Method for detecting intraperitoneal free cancer cells

A total of 192 patients undergoing gastrectomy for gastric cancer between January 1984 and December 1987 were studied. In these patients, the peritoneal cavity was washed with 100 ml of physiological saline (kept at 37°C) immediately after laparotomy using the method of Iizuka and colleagues[8]. After washing, 50 ml of fluid were aspirated and immediately centrifuged at 2000 r.p.m. for 5 min. The nucleated cell layer was smeared on glass slides, stained with Giemsa and Papanicolaou stain, and assessed and classified by experienced cytologists.

Results

Survival rates following curative gastrectomy in relation to the depth of cancer invasion

There was a strong relationship between the 5-year survival rate in patients undergoing curative gastrectomy and the depth of invasion by the primary tumour (*Figure 1*). The 5-year survival rates for patients with S_0, S_1, S_2 and S_3 were 89·6, 61·3, 42·1 and 28·9 per cent, respectively (S_0 *versus* S_1, S_1 *versus* S_2: $P<0.001$).

With regard to histopathological presence or absence of serosal invasion, the 5-year survival rate was found to be 75·9 per cent for 385 patients with no invasion and 47·1 per cent for 136 patients with invasion ($P<0.001$, *Figure 2*).

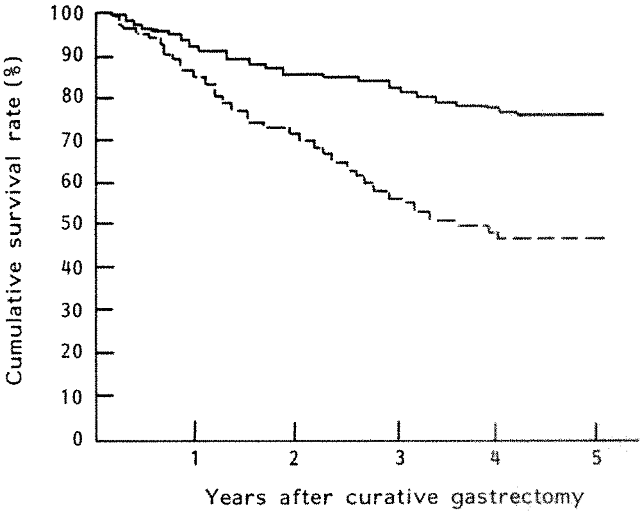
Five-year survival rates for patients with undifferentiated tumours were lower than differentiated tumours in serosal invasive cases, although the difference was not significant (data not shown).

Relationship between serosal infiltration and intraperitoneal free cancer cells

Of 192 gastric cancer patients without macroscopic peritoneal dissemination and/or liver metastasis, the percentage with exfoliated cancer cells in the peritoneal cavity was 0 per cent in the S_0 group, 3·3 per cent in the S_1 group, 15·7 per cent in the S_2 group and 34·8 per cent in the S_3 group. The difference between the S_3 group and the other groups was statistically significant (S_3 *versus* S_2, $P<0.05$; S_3 *versus* S_1/S_0, $P<0.01$).

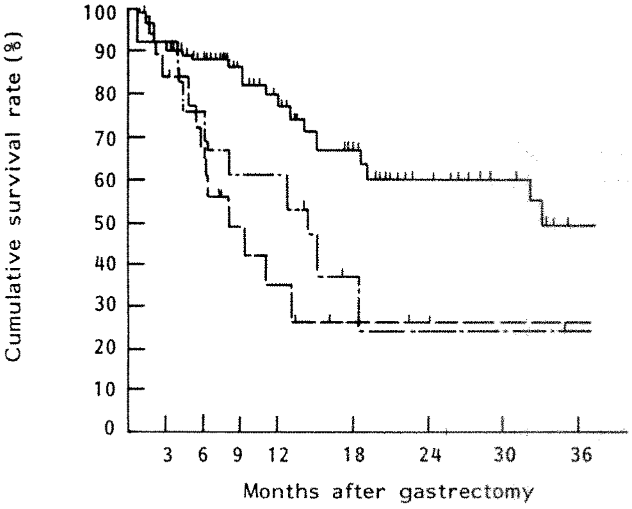
When the relationship between the histological type of the primary tumour and the presence of exfoliated cancer cells in the peritoneal cavity was investigated, it was found that of 93 S_2 and S_3 patients, 30 per cent of the 53 with undifferentiated adenocarcinoma and 13·2 per cent of the 40 with differentiated adenocarcinoma, were positive for such free cancer cells ($P<0.05$).

Of 93 S_2 and S_3 patients, who did not macroscopically exhibit peritoneal dissemination, the 74 without free cancer cells in the peritoneal cavity had a significantly higher 3-year survival rate than did the remainder who were positive for free cancer cells ($P<0.01$, *Figure 3*). The 3-year survival rate was also



—— 385	281	209	162	128	100
--- 136	95	70	48	39	34

Figure 2 *Cumulative survival rates in cases of curative gastrectomy related to prognostic serosal invasion (total number of patients = 521); —— ps(−) (385); --- ps(+) (136);* $P<0.001$. *Number of patients eligible for analysis at each time point are shown*



* ——— 74	60	45	18	6
** — — — 19	13	5	1	1
*** —·— 13	10	8	2	1

Figure 3 *Cumulative survival rates of gastrectomized patients with serosal invasion as a function of peritoneal dissemination and presence of free cancer cells in the peritoneal cavity (total number of patients = 106); —— S_2, S_3, P_0, negative for free cancer cells (74); --- S_2, S_3, P_0, positive for free cancer cells (19); -·-·- S_2, S_3, $P(+)$, (13);* $P<0.05$ (* versus ***) $P<0.01$ (* versus **). *Number of patients eligible for analysis at each time point are shown*

significantly higher in this group of 74 patients (P_0, no free cancer cells) than in the 13 patients with obvious peritoneal dissemination ($P(+)$, $P<0{\cdot}05$). However, there was no significant difference, in terms of longevity measured 3 years after gastrectomy, between P_0 cases positive for free cancer cells and $P\ (+)$ cases.

Serosal invasion and lymph node metastasis

The relationship between the degree of serosal invasion and nodal involvement is presented in *Figure 4*. As the S number increased, so did the frequency of lymph node involvement. Five-year survival rates for S_2, S_3 cases classified as n_0, n_1 and n_2 cases were 67·9, 32·8 and 32·1 per cent respectively. There were significant differences in the survival rates between n_0, n_1 and n_2 groups (*Figure 5*). A similar survival pattern for different stages of lymph node metastasis was seen after curative gastrectomy for cancer in patients with histologically proved serosal invasion, indicating that the histological evidence of serosal invasion had the same prognostic significance as depth of invasion (S_2, S_3).

Relationship between the mode of the spread of cancer into the lymph nodes and serosal invasion

Of the 66 positive lymph nodes in which cancer was limited to the mucosa and submucosa, 36 exhibited type I metastasis. Types I, II and III were of almost equal incidence (28·8, 35·9 and 34·2 per cent respectively) in cases where cancer had invaded the muscular layer. However, in patients with serosal invasion that had been defined histologically, the frequencies of types I and II metastasis were low and high (14·5 and 39·0 per cent respectively), while those of types III and IV were intermediate and nearly equal. It is thus evident that the spread of cancer cells into the lymph nodes becomes more extensive with increased incidence of infiltration of the perinodal areolar tissue, as the depth of cancer invasion increases (*Table 1*).

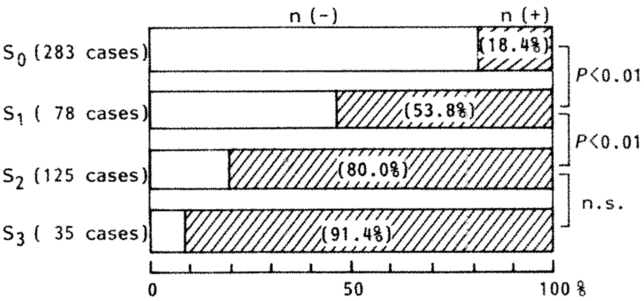


Figure 4 *Serosal invasion and lymph node metastasis in gastrectomized cases. n(−), no metastasis to lymph nodes; n(+) presence of lymph node metastasis*

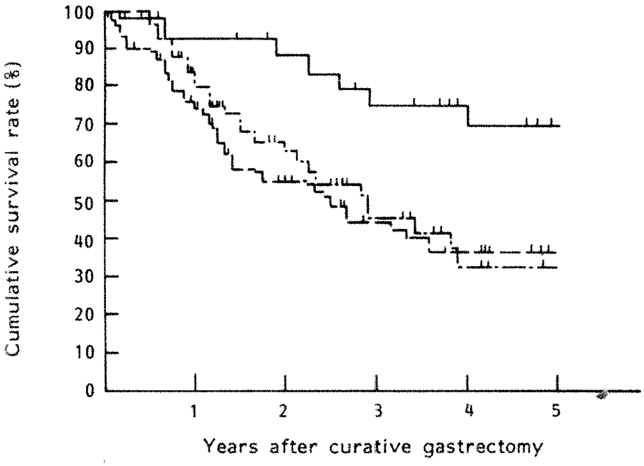
Discussion

In Japan, the diagnosis of early gastric cancer has become more accurate recently, and the operative mortality rates for curative gastrectomy are very low[9]. Nevertheless, recurrence is common despite curative resection, and many such patients with recurrence have infiltration of the serosa at the time of resection. Kaibara *et al.*[10], have shown a correlation between the area of serosal invasion and survival. In this study, significance of serosal invasion was analysed according to histopathological findings of the tumours.

The higher the S category, the worse the 5-year survival rate. Most of the recurrent forms of cancer invading the serosa resulted from intraperitoneal dissemination and most of the patients died within 2 years of operation. In order to improve these statistics, considerable effort is required for early diagnosis. Diagnosis at an earlier pathological stage also reduces operative mortality and postoperative morbidity rates.

From the results obtained in this study, patients with negligible or no serosal invasion had a more favourable prognosis when there was no lymph node metastasis; 5-year survival rate progressively decreased with increasing lymph node involvement. Thus, the higher the S and n values, the lower the 5-year survival rate. Many reports have also shown that the depth of invasion has a marked effect on prognosis; if the cancer extends to the muscularis propria or deeper, the prognosis then becomes progressively worse[1-3].

Of the many factors relevant to survival after curative



*——	28	26	23	19	15	12
**— — —	74	50	34	22	16	9
***— · —	54	41	24	14	7	5

Figure 5 *Cumulative survival rates in gastrectomized cases with serosal invasion (S_2, S_3) as a function of different degrees of lymph node metastasis (total number of patients = 156);* —— *n_0 (28);* — — — *n_1 (74);* — · — · — *n_2 (54);* $P<0{\cdot}001$ (* versus **), $P<0{\cdot}05$ (* versus ***). *Number of patients eligible for analysis at each time point are shown*

Table 1 *Histological pattern of lymph node metastasis for different depth of primary cancer invasion*

Depth of primary invasion		Type of lymph node metastasis								
		I		II		III		IV		Total
No serosal invasion detected microscopically	m, sm (27 cases)	36 (54·5)		11 (16·7)		17 (25·8)		2 (3·0)		66 (100)
			$P<0{\cdot}01$		$P<0{\cdot}01$		n.s.		$P<0{\cdot}01$	
	pm (36 cases)	53 (28·8)		66 (35·9)		63 (34·2)		2 (1·1)		184 (100)
			$P<0{\cdot}01$		n.s.		$P<0{\cdot}01$		$P<0{\cdot}01$	
Serosal invasion detected microscopically	se, si, sei (29 cases)	72 (14·5)		193 (39·0)		119 (24·1)		111 (22·4)		495 (100)

m, invasion of the mucosa; sm, invasion of the submucosa; pm, invasion of the muscularis propria; se, invasion of the serosal surface and exposure to the peritoneal cavity; si, invasion of the neighbouring tissue; and sei, the coexistence of se and si. Values in parentheses are percentages gastrectomy, the most important are considered to be the presence of serosal invasion and lymph node metastasis with peritoneal dissemination, while hepatic metastasis is not relevant[3].

The cause of intraperitoneal dissemination is, at first, cancer infiltration from the serosa. The grade of serosal invasion was correlated with the risk of finding intraperitoneal free cancer cells. It follows that patients with serosal invasion are at risk of intraperitoneal recurrence. In our P_0 patients, those with free cancer cells had lower survival rates than those without (*Figure 3*), so that free cancer cells were an important prognostic factor as well as macroscopic peritoneal dissemination, P (+).

A second factor relating to intraperitoneal dissemination is the possibility of cancer infiltration from metastatic lymph nodes. We investigated the types of lymph node metastasis. In cancers with serosal invasion, 111 (22·4 per cent) of the 495 lymph nodes were classified as type IV, which was significantly higher than in cases with no serosal invasion (*Table 1*). Therefore, we conclude that serosal invasion cases have many lymph nodes in which cancer cells invade perinodal fatty tissues, and that these cases have the potential for peritoneal dissemination.

However it is worth noting that free cancer cells in the peritoneal cavity were found more frequently in cases of undifferentiated carcinoma, and that the survival rates for patients with undifferentiated tumours were lower than for those with differentiated tumours. There are many studies showing that undifferentiated tumours often relapse into forms of peritoneal dissemination. This can be explained by the fact that free cancer cells in the peritoneal cavity are found more frequently in patients with undifferentiated tumours and that free cancer cells may progress to dissemination. Such findings are in agreement with those presented by Iizuka *et al.*[8], which suggest that an increase in the number of detached cells may be attributed to decreased mutual adhesiveness of undifferentiated cancer cells. Further study is required to confirm this hypothesis.

A large proportion of free cancer cells found in peritoneal washings has been shown to be viable using ^{3}H-thymidine uptake and enzymatic staining procedures[8,11]. Furthermore, it has been reported that some of these cancer cells may retain considerable viability even after the intraperitoneal administration of mitomycin C[11]. The presence of free cancer cells in the peritoneal cavity of gastric cancer patients[12,13] has been previously demonstrated and the prognosis for such patients is known to be poor[12,14]. However, further research is needed to elucidate the most effective carcinostatic treatment for the prevention of intraperitoneal dissemination of cancer. Since the exact mechanism responsible for cancer cell implantation and proliferation in the peritoneum remains unclear, more studies along these lines would be useful in preventing cancer recurrence after gastrectomy.

The unfavourable prognosis in gastric cancer patients with serosal invasion, even following curative gastrectomy, is probably related both to the presence of viable free cancer cells that spread through the serosal and perinodal areolar infiltration, as well as the biological character and histological type of these cancer cells.

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Obstructive jaundice and wound healing

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Wound healing was studied in 95 jaundiced patients and 123 anicteric patients using skin prolylhydroxylase activity as an index of collagen synthesis. The mean(s.d.) value of skin prolylhydroxylase activity in jaundiced patients was significantly lower than that of controls in the preoperative period (40·1(19·2) versus *369·2(32·2) c.p.m./mg protein, respectively,* $P<0.001$*). Before operation there was a significant difference between patients with benign or malignant obstruction of the biliary tree (55·0(12·3)* versus *25·2(10·4) c.p.m./mg protein, respectively,* $P<0.05$*). In patients with benign obstruction skin prolylhydroxylase activity returned to normal values (326·3(53·1) c.p.m./mg protein,* $P<0.001$ versus *preoperative values), while in patients with malignant lesions skin prolylhydroxylase activity increased significantly with respect to the preoperative period (25·2(10·4)* versus *82·9(14·3) c.p.m./mg protein,* $P<0.01$*) but was still below normal values. Abdominal wound dehiscence was more common in jaundiced patients (six of 95) than in the anicteric group (two of 123). This complication appeared to be associated with a low skin prolylhydroxylase activity.*

Keywords: Collagen synthesis, obstructive jaundice, wound healing

Normal collagen synthesis is essential for the development of tissue tensile strength. Clinical and experimental data show that obstructive jaundice is associated with delayed wound healing[1–5], although recent studies have suggested that impaired healing in jaundiced patients is not caused by jaundice *per se* but is due to the associated malnutrition and/or malignancy[6–9].

This study was carried out to measure skin prolylhydroxylase activity (SPHA) as an index of collagen synthesis in a control group and in jaundiced patients, and to correlate SPHA levels with the incidence of abdominal wound dehiscence.

Patients and methods

Patients and controls

We studied 95 patients (53 men and 42 women; mean age 56·1 years, range 35–82 years) with extrahepatic obstructive jaundice (plasma bilirubin >50 μmol/l, normal range 2–17 μmol/l) who underwent surgery for relief of bile duct obstruction, during the period from April 1983 to December 1987, in the Department of Surgery at the University of Barcelona. The cause of the obstruction was malignant disease in 61 patients and benign disease in 34. Jaundice was relieved in all patients by the operative procedure (resection, biliary diversion or transtumoral cannulation). The control group consisted of 123 anicteric patients (31 men and 92 women, mean age 57·3 years, range 30–80 years) undergoing cholecystectomy during the same period. Surgical procedures were performed by the authors, all of them staff members of the department. Plasma bilirubin, total protein and albumin levels were determined in patients and controls by routine laboratory procedures.

Study protocol

A specimen of skin was removed from the edge of a subcostal or upper midline incision at the time of the operation. In 75 previously jaundiced patients it was feasible to take, under local anaesthesia, a further specimen of skin from the anterior abdominal wall when plasma bilirubin levels had returned to normal (<17·1 μmol/l). Fat was carefully removed from the skin specimen, which was stored in codified Nunc tubes (InterMed, Kamstrup, Denmark) at −20°C.

Skin prolylhydroxylase activity

SPHA was measured as reported by Than Than *et al.*[10,11] and McGee *et al.*[12]. Briefly, a substrate was prepared with [^{3}H]-4-proline by a modification of the method of Hutton *et al.*[13]. The skin specimen was homogenized in a buffer solution, centrifuged, and the supernatant was immediately incubated with labelled substrate in the presence of ferrous ammonium sulphate, α-ketoglutarate and ascorbic acid. After incubation, the solution was centrifuged and the supernatant was distilled. SPHA was measured by the tritium release technique and was expressed as counts per minute per milligram of protein (c.p.m./mg protein). Protein was measured by the method of Lowry *et al.*[14]. Maximum intra-assay variation coefficient was 8·4 per cent[15].

Statistical analysis

All data are reported as mean(s.d.). The frequency of wound dehiscence was compared using the χ^2 test, or Fisher's exact test when numbers were small. A non-parametric test (Mann–Whitney *U* test) was applied to SPHA measurements. Linear regression analysis was used when appropriate.

The study was approved by the University of Barcelona's Committee on Human Research in Medical Sciences on 10 February 1983, and informed consent was obtained from all patients.

Results

In the control group the mean(s.d.) value of SPHA was 369·2(32·2) c.p.m./mg protein. At the time of the surgical procedure, the mean(s.d.) value of SPHA in the jaundiced patients was 40·1(19·2) c.p.m./mg protein, significantly lower than the mean value of controls ($P<0.001$). No significant correlation was found between SPHA and plasma bilirubin, total protein or albumin levels ($r=-0.09$, 0·27 and 0·23, respectively). In the postoperative period, when plasma bilirubin levels had reached normal values, SPHA increased in previously jaundiced patients from 40·1(19·2) to 204·6(42·1) c.p.m./mg protein ($P<0.01$).

The 95 icteric patients were divided into two groups: those who had malignant obstruction ($n=61$), and those who had benign lesions ($n=34$). The preoperative values were significantly different in the two groups (55·0(12·3) c.p.m./mg protein in benign obstruction *versus* 25·2(10·4) c.p.m./mg protein in neoplastic obstruction; $P<0.05$) (*Figure 1*). The changes in SPHA in the postoperative period were also significantly different in both groups. While the SPHA increase in patients with malignant disease was only from 25·2(10·4) to 82·9(14·3) c.p.m./mg protein ($P<0.01$), in patients with benign obstructive jaundice SPHA increased from 55·0(12·3) to

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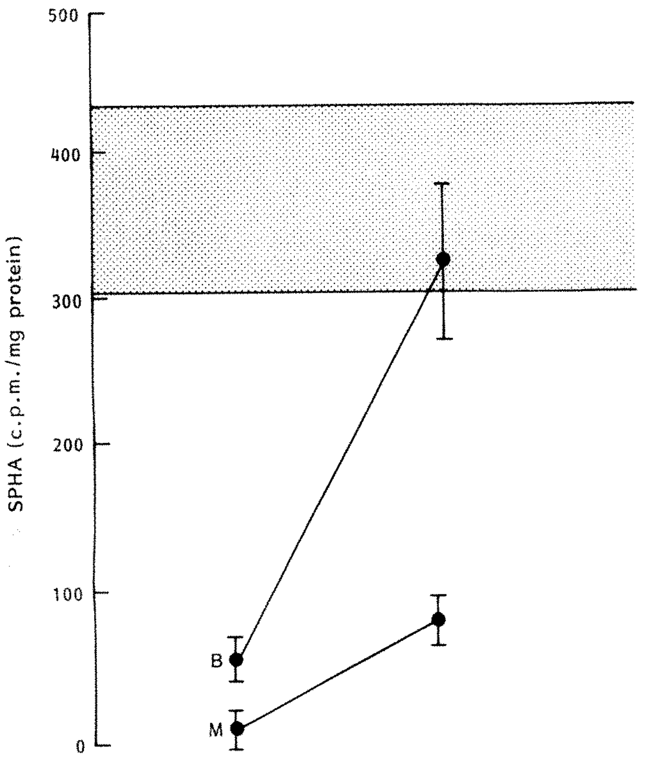

Figure 1 *Skin prolylhydroxylase (SPHA) activity variations in preoperative and postoperative periods in jaundiced patients with benign (B) or malignant (M) biliary obstruction. Note that the mean value in jaundiced patients with benign obstruction returns to normal (shaded area) in the postoperative period*

326·3(53·1) c.p.m./mg protein ($P<0{\cdot}001$) (*Figure 1*). Although plasma total protein or albumin levels were lower in patients with malignant obstruction than in patients with benign disease (65·4(7·4) *versus* 73·0(4·5) g/l and 32·5(3·5) *versus* 39·5(3·5) g/l, respectively), these differences did not reach statistical significance. Moreover, no correlation could be demonstrated between variations in these values and SPHA levels ($r=0{\cdot}37$ and 0·34, respectively).

Eight patients developed a wound dehiscence. This complication was more common in jaundiced patients (six of 95 patients, 6 per cent) than in the anicteric group (two of 123 patients, 2 per cent), but the difference did not reach statistical significance. All patients with wound dehiscence in the jaundiced group had malignant biliary obstruction (six of 61 patients, 10 per cent). They all had preoperative SPHA below normal limits (taken as within two standard deviations of the control levels), but the two patients in the control group with wound dehiscence also had low SPHA (163 and 180 c.p.m./mg protein, respectively). In addition, all patients with wound dehiscence from the group with obstructive jaundice had postoperative SPHA below 85 c.p.m./mg protein (mean(s.d.) 53·1(17·8) c.p.m./mg protein) (*Figure 2*). The incidence of wound dehiscence was not related to performance of the operation by a particular surgeon.

Discussion

Collagen contains two amino acids not found to any extent in other mammalian proteins, namely hydroxyproline and hydroxylysine. Prolylhydroxylase is a hydroxylating enzyme necessary for incorporation of proline into the growing peptide chain, and its activity has been used as an index of collagen synthesis[10,11]. In the present study we have confirmed that obstructive jaundice is associated with a significant reduction in SPHA. Similar results have been reported by Than Than *et al.*[10] but in our study we also measured postoperative values of SPHA when serum bilirubin had reached normal levels after surgical relief of biliary obstruction. The data obtained allow us to develop the conclusions arising from the work of Than Than *et al.*[10]. Contrary to their findings, we detected significant differences in the preoperative period between jaundiced patients with and without malignant biliary obstruction. Additionally, we observed a different evolution of SPHA levels after surgical relief of biliary obstruction. Thus, while SPHA levels in patients with either type of biliary obstruction were below those found in controls, they were significantly lower in patients with malignant obstruction when compared with those with benign lesions. On the other hand, after surgical relief of biliary obstruction and a return to normal serum bilirubin levels, SPHA returned to normal limits in patients with benign jaundice while remaining at much lower levels in those with malignant obstruction. Our study did not address the question of the mechanism by which jaundice leads to a reduction of SPHA levels in icteric patients, but it is likely that some substance in the retained bile plays an important role in decreasing collagen synthesis, as inferred by the return to normal of SPHA in most patients after resolution of biliary stasis.

Surgery in patients with obstructive jaundice is associated with a high postoperative morbidity[9]. Delayed wound healing and a high incidence of wound dehiscence and incisional hernias have been observed in patients in whom operations had been carried out to relieve obstructive jaundice[3,4,6–8,16,17]. There is

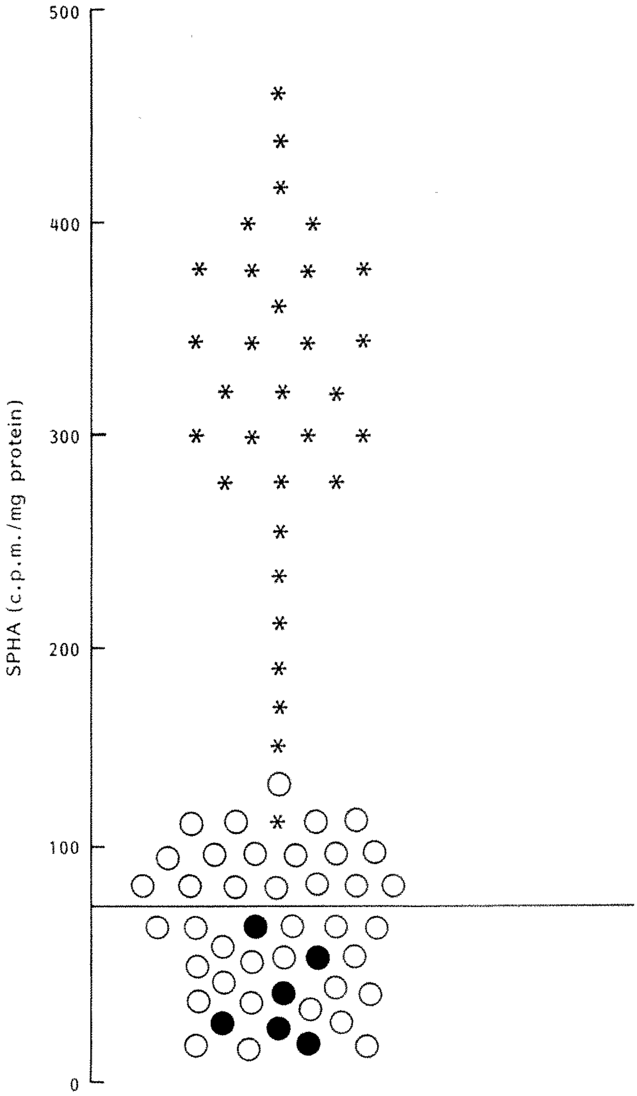

Figure 2 *Postoperative values of skin prolylhydroxylase (SPHA) activity in 75 jaundiced patients with benign (*) or malignant (○) biliary obstruction. Shaded circles represent patients with abdominal wound dehiscence, all of whom had SPHA below 85 c.p.m./mg protein*

some evidence of biochemical disturbances in the healing wounds of jaundiced animals as collagen accumulates more slowly in such wounds[2], but jaundiced patients may have several abnormalities other than hyperbilirubinaemia which affect wound healing, notably malignancy and malnutrition[9]. Hypoproteinaemia has been implicated as one cause of wound disruption by prolonging the lag phase and preventing onset of the fibroplastic phase of wound healing processes. However, the decreased rate of wound healing is not well correlated with plasma protein levels[18]. Although serum albumin concentration is lower in the malignant group than in the benign group (although the difference is not statistically significant), no correlations between plasma protein or albumin and SPHA levels in jaundiced patients (malignant or benign obstruction) or in control patients were demonstrated. In the present study wound dehiscence was more common, but not significantly so, in jaundiced patients than in an anicteric control group, and was particularly troublesome in malignant obstruction. All the patients with wound dehiscence had SPHA below normal limits in the preoperative period, and this did not rise above 85 c.p.m./mg protein after operation in any of those with previous jaundice. This level may be considered as a critical one, below which the incidence of wound dehiscence may be close to 25 per cent.

In conclusion, SPHA estimated as a marker of collagen synthesis is reduced in patients with obstructive jaundice. This feature may be related to the high incidence of wound dehiscence observed in jaundiced patients.

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Splenectomy for hypersplenism in chronic lymphocytic leukaemia and malignant non-Hodgkin's lymphoma

Between 1 January 1980 and 31 July 1988, 62 patients with chronic lymphocytic leukaemia (CLL) or malignant non-Hodgkin's lymphoma (NHL) were splenectomized for splenomegaly and presumed hypersplenism. All patients except one had splenomegaly (mean(s.d.) weight 1585(872) g, range 150–4300 g) and 34 had massive splenomegaly (> 1500 g). Forty-nine patients had platelet counts $< 100 \times 10^9/l$ and 16 patients had anaemia with haemoglobin levels < 10 g/dl. White cell counts were $< 3 \times 10^9/l$ in six NHL patients. Fifteen patients had bicytopenia, and three NHL patients had tricytopenia. The selected group of 62 patients underwent splenectomy largely because of failure to respond to medical therapy (39 patients) or inability to tolerate or start adequate chemotherapy because of very low blood counts (11 patients). There was one postoperative death, and a 29 per cent morbidity rate. The response rate was 89 per cent in the first month after splenectomy and 39 patients (63 per cent) had a continuing complete response with a median follow-up of 26 months (range 3–96 months). Twelve patients (10 with CLL) received no further therapy after splenectomy. Seven patients failed to respond and 15 relapsed after splenectomy. These 22 patients could be distinguished on the basis of: (1) lower average preoperative platelet counts ($P < 0{\cdot}007$), postoperative platelet counts ($P < 0{\cdot}001$), and postoperative rise in platelets ($P < 0{\cdot}004$); (2) lower average spleen weight ($P < 0{\cdot}052$); (3) preoperative chemotherapy ($P < 0{\cdot}044$). However preoperative and postoperative platelet counts were the only two variables selected by stepwise regression analysis ($P < 0{\cdot}05$ and $P < 0{\cdot}01$, respectively). Bone marrow failure did not preclude complete response after splenectomy. Long-term survivors emerged from the group of patients with continuing complete response. Of the seven patients who failed to respond, five died with a median survival of 4 months, and of the 15 patients who relapsed after splenectomy, 13 died, with a median survival of 6 months after relapse and 18 months after splenectomy. Thus, splenectomy may be an effective palliation for both CLL and NHL patients with splenomegaly and hypersplenism.

Keywords: Splenectomy, hypersplenism, chronic lymphocytic leukaemia, non-Hodgkin's lymphoma

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The therapeutic value of splenectomy in the management of malignant lymphoma has been controversial for years[1–5]. Bulk symptoms and haematological defects are common complications of splenic neoplastic involvement that appear at some time in the disease process of both chronic lymphocytic leukaemia (CLL) and non-Hodgkin's lymphoma (NHL). Persistent cytopenia is often the result of splenic overactivity, bone marrow infiltration and previous chemotherapy. Hypersplenism is usually presumed and splenectomy remains the only means of determining with confidence the contribution of the spleen, despite the use of preoperative tests for survival and sequestration of erythrocytes and platelets[6–9]. Bone marrow disease may not necessarily be a contraindication to splenectomy. The Oxford study showed haematological remission in 80 per cent of such cases[7–10]. Autoimmune cytopenia, especially refractory autoimmune anemia, is also a common haematological abnormality in CLL and NHL. Complete haematological response and long-term remission after splenectomy have been reported in patients not responding to steroids[11–14], but the relapse rate is high[9] and patients who are Coombs' positive are often poor or transient responders[15]. The few splenectomized patients in our institute with evidence of autoimmunity have been excluded from this report.

The unpredictable haematological response to splenectomy and the poor survival benefit reported in several series weigh against surgery[11,14,16]. However, in these series splenectomy was often performed as a salvage procedure with poor results. The authors[17,18] and others have reported a satisfactory correction of haematological status and a possible survival benefit in both CLL and NHL responder patients with presumed hypersplenism who are acceptable surgical risks[1,7,8,12,13,19–22].

The medical records of 62 patients who had splenomegaly and presumed hypersplenism were reviewed in an attempt to

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Table 1 *Preoperative and postoperative haematological findings for 62 splenectomized patients with chronic lymphocytic leukaemia and non-Hodgkin's lymphoma*

	Chronic lymphocytic leukaemia ($n=44$)		Non-Hodgkin's lymphoma ($n=18$)	
	Mean(s.d.)	Range	Mean(s.d.)	Range
Preoperative data				
Haemoglobin (g/dl)	10·9(1·83)	6·6–15·5	11·4(1·4)	9·1–14·2
Platelets ($\times 10^9$/l)	71·5(37·3)	10·0–194	86·6(27·7)	20·0–130
White cells ($\times 10^9$/l)	123·5(189·6)	4·0–1100	5·0(3·3)	1·3–15·5
Postoperative data				
Haemoglobin (g/dl)	12·2(1·34)	9·4–14·7	12·6(1·7)	9·3–15·3
Platelets ($\times 10^9$/l)	303·0(165·0)	31·0–761	380·0(167)	45–632
White cells ($\times 10^9$/l)	95·9(144·3)	8·2–850	11·0(6·2)	1·9–22

identify the significant factors in predicting any response and its duration, and to determine the impact of splenectomy on the subsequent clinical course of the disease.

Patients and methods

Between 1 January 1980 and 31 July 1988, 62 of 85 splenectomized patients with CLL or NHL had splenomegaly and presumed hypersplenism. The medical records of all patients were reviewed retrospectively from 1980 and the data have been collected prospectively since mid-1985. These include histopathological features, duration of disease, preoperative treatment, indications for splenectomy, intra-operative status, and postoperative course with subsequent progress of the disease. Life-span and sequestration tests of erythrocytes and platelets, with or without immunoglobulin G coating, were studied before surgery in only a few patients. Increased splenic activity was considered as a possible factor in any patient with anaemia (haemoglobin) level < 10 g/dl), thrombocytopenia (platelet count $< 100 \times 10^9$/l), leukopenia (white cell count $< 3 \times 10^9$/l) or any combination of these. Forty-four CLL patients with stage C disease[23] and 18 NHL patients met these haematomological criteria and entered the study. Patients were defined as having a haematological response only if all haematological abnormalities were corrected after splenectomy. Patients were followed to assess relapse and subsequent clinical course of disease. All patients received antipneumococcal vaccination before surgery and long-term oral penicillin after surgery.

There were 35 men and 27 women with a mean(s.d.) age of 60(11) years (range 21–80 years). The mean interval between diagnosis and surgery was 44·8(37) months (range 1–172 months) for CLL and 12(22) months (range 1–74 months) for NHL patients. All patients except one had splenomegaly, with a mean spleen weight of 1585(872) g (range 150–4300 g). Thirty-four patients had massive splenomegaly as defined by Goldstone[24], i.e. > 1500 g. *Table 1* shows the mean preoperative platelet counts, haemoglobin levels and white cell counts of the 62 patients. The preoperative haematological data for each patient are shown in *Figures 1* and *2*. Fifteen patients (eight CLL and seven NHL) had bicytopenia, and three NHL patients had tricytopenia. Bone marrow films showed rich or very rich cellularity in all CLL patients. Megakaryocytes were in the normal range in 22 patients, high in five, low or very low in 12, and zero in five. Massive lymphocytic infiltration was observed in all patients. Ten NHL patients had bone marrow disease and widespread nodal involvement. Bone marrow involvement was not considered as a contraindication to splenectomy. In 43 patients CLL involved B cells. One patient had prolymphocytic leukaemia. Seven patients had NHL of high grade malignancy, three patients had intermediate grade and eight had low grade malignant disease[25].

Indications for splenectomy

Twelve of the 62 patients had undergone no other form of therapy before splenectomy. Seven of the 12 had NHL and underwent splenectomy both for diagnosis and therapy. Fifty patients (39 CLL, 11 NHL) had received chemotherapy and/or corticosteroids. Only one CLL patient had had previous splenic irradiation. The indications for splenectomy in these patients were failure to respond to medical therapy (33 CLL and six NHL) or inability to tolerate or start adequate chemotherapy because of very low blood counts (six advanced CLL and five NHL).

Operative procedure

All patients had elective splenectomy which was performed through a generous midline incision in 50 patients or a subcostal incision in 12

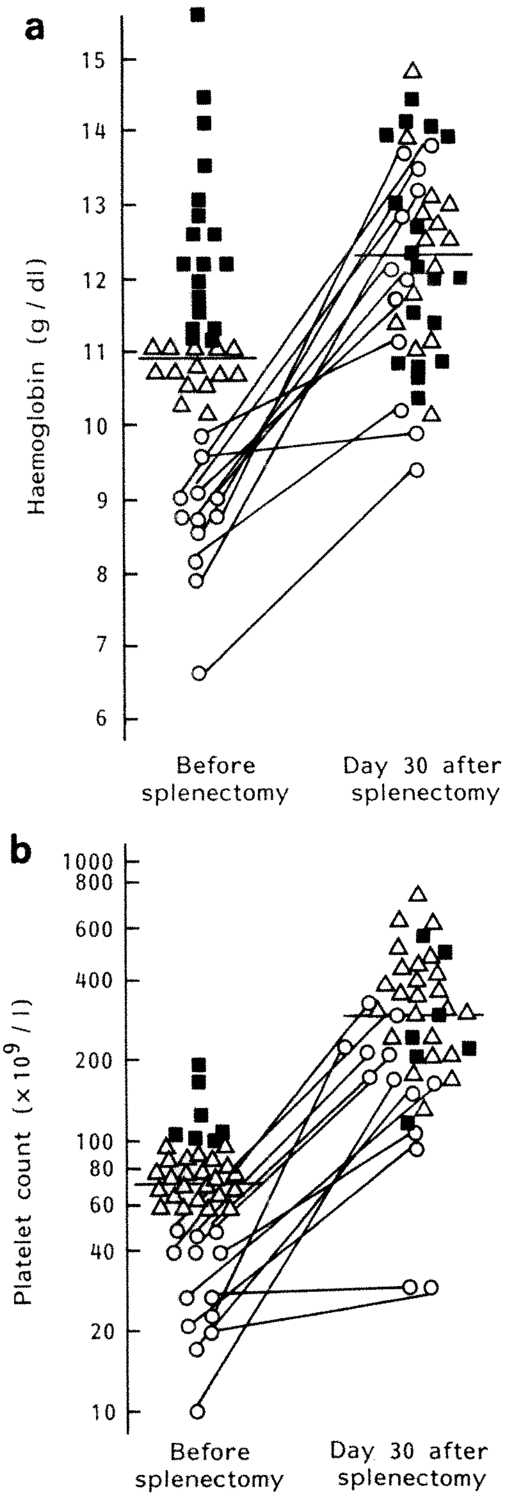

Figure 1 *Preoperative and postoperative haematological data for 44 patients with chronic lymphocytic leukaemia* **a** *haemoglobin level (preoperative levels: ○ < 10 g/dl; △ $\leqslant 11$ g/dl; ■ > 11 g/dl), Wilcoxon test: $P < 0{\cdot}001$ and* **b** platelet count *(preoperative levels: ○ $< 50 \times 10^9$/l; △ $< 100 \times 10^9$/l; ■ $\geqslant 100 \times 10^9$/l), Wilcoxon test: $P < 0{\cdot}0001$. Bars are means and lines connect the data of patients with haemoglobin levels < 10 g/dl and patients with platelet counts $< 50 \times 10^9$/l*

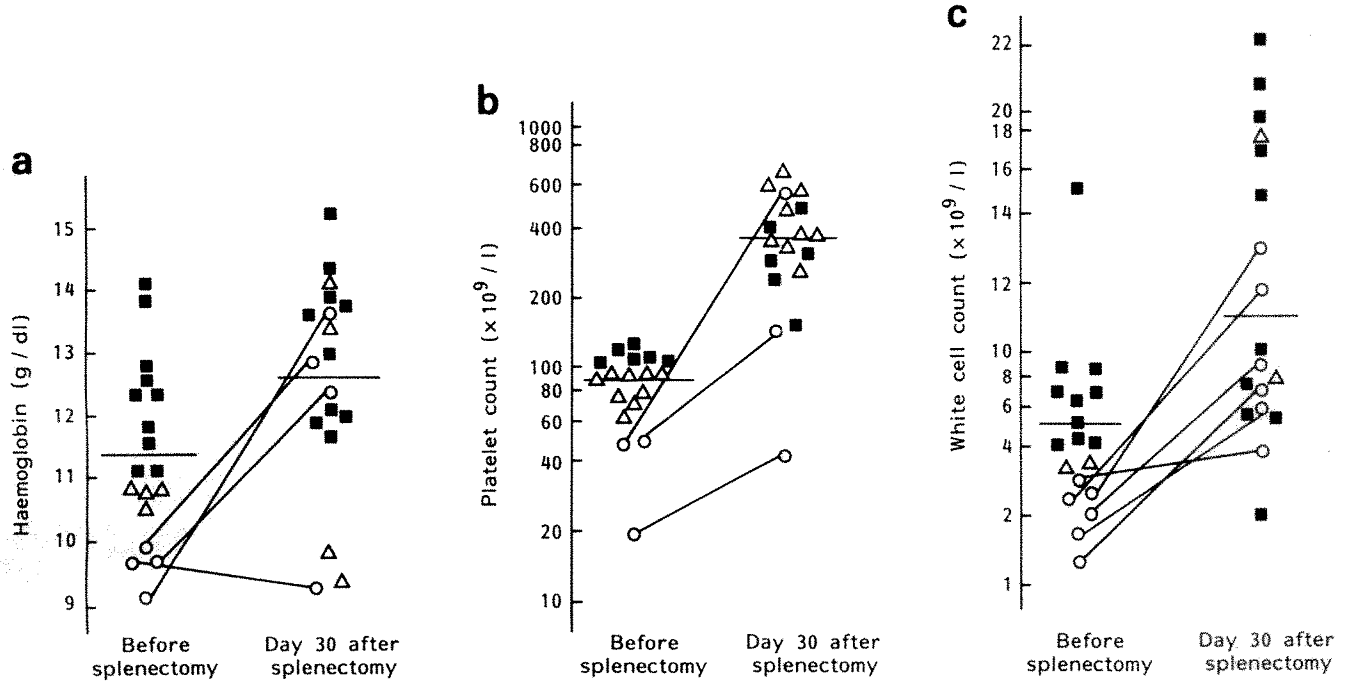

Figure 2 *Preoperative and postoperative haematological data for 18 patients with non-Hodgkin's lymphoma* **a** *haemoglobin levels (preoperative levels:* ○ < 10 *g/dl;* △ $\leqslant 11$ *g/dl;* ■ > 11 *g/dl), Wilcoxon test:* $P < 0{\cdot}05$; **b** platelet counts (preoperative levels: ○ $< 50 \times 10^9$/l; △ $< 100 \times 10^9$/l; ■ $\geqslant 100 \times 10^9$/l), *Wilcoxon test:* $P < 0{\cdot}0001$; **c** *white cells count (preoperative levels:* ○ $< 3 \times 10^9$/l; △ $\leqslant 3{\cdot}5 \times 10^9$/l; ■ $> 3{\cdot}5 \times 10^9$/l), *Wilcoxon test:* $P < 0{\cdot}001$. *Bars are means and lines connect the data of patients with haemoglobin levels* < 10 *g/dl, patients with platelet counts* $< 50 \times 10^9$/l, *and patients with white cell counts* $< 3 \times 10^9$/l

Table 2 *Postoperative mortality and morbidity for 62 splenectomized patients with chronic lymphocytic leukaemia and non-Hodgkin's lymphoma*

	Chronic lymphocytic leukaemia ($n = 44$)	Non-Hodgkin's lymphoma ($n = 18$)	Total ($n = 62$)
Mortality			
Pulmonary embolism	1	–	1
Morbidity			
Pneumonia	1	–	1
Pleural effusion	2	1	3
Postoperative haemorrhage	3	–	3
Lymphangitis	1	–	1
Wound infection	1	–	1
Fever of undetermined origin	6	2	8
Pancreatic fistula	1	–	1
Total morbidity*	15 (34)	3 (17)	18 (29)

Values in parentheses are percentages. * Chronic lymphocytic leukaemia *versus* non-Hodgkin's lymphoma, χ^2 with continuity correction; 0·132, $P = 0{\cdot}287$

patients with wide costal margin. The gastrosplenic ligament was first divided and the splenic artery and vein(s) ligated before mobilization of the spleen. Fifteen patients had *en bloc* resection of the spleen and surrounding tumour mass with a short necessary distal pancreatectomy by transection with linear staple devices. The splenic bed was always drained. Lymph node, liver and bone marrow biopsies were usually performed.

Statistical analysis

All normative values reported are given as mean(s.d.). The lowest preoperative and postoperative haematological data (day 30) were submitted to the Wilcoxon rank sum test. Student's t test for paired and unpaired values was used for comparison of means. The χ^2 test with continuity correction was used for comparison of percentages, unless expected values were less than five, in which case Fisher's exact test was used. For study of the relationship between the spleen weight and differences between preoperative and postoperative haematological values (rise in haemoglobin, platelets and white cells), a linear regression analysis was performed using the differences in the sums of squares. The significant factors in predicting a continuing complete response determined by univariate analysis were submitted to a stepwise regression analysis. Raw survival rate was calculated on 31 September 1988. Survival was plotted from the date of splenectomy and diagnosis. Two NHL patients lost from follow-up at 26 and 52 months after surgery were considered as having died of the disease. Cumulative survival curves and cumulative risk (of relapse of cytopenia) curves after splenectomy were drawn according to Kaplan and Meier[26]. Comparison between groups was achieved using the log rank test. Statistical significance was accepted at the 5 per cent level.

Results

Mortality and morbidity of splenectomy

One patient died of massive pulmonary embolism at day 30. Complications occurred in 18 patients, including eight fevers of unknown origin (*Table 2*). Three patients had second successful operations, two for postoperative haemorrhage and one for pancreatic fistula 5 months after splenectomy. The mean length of hospital stay for survivors was 16(6·2) days (range 8–37 days).

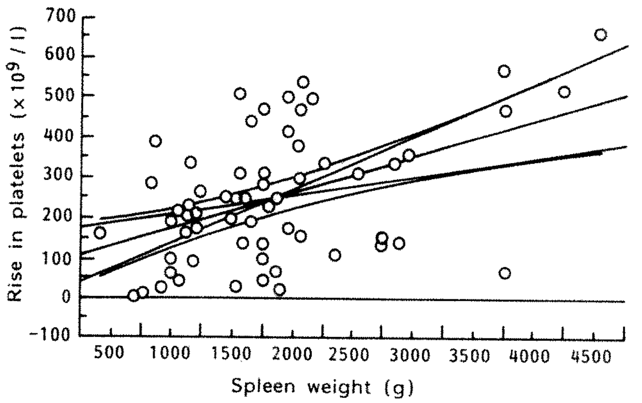

Figure 3 *Linear regression analysis between spleen weight (g) and postoperative rise in platelets* ($\times 10^9$/l) *at day 30* (n = 62 *patients*): $P<0{\cdot}0001$ ($r=0{\cdot}475$; F-*test* = 17·488). *Significance for the subgroups are:* $P<0{\cdot}0007$ *for chronic lymphocytic leukaemia* ($r=0{\cdot}489$, F-*test* = 13·235) *and* $P<0{\cdot}04$ *for non-Hodgkin's lymphoma* ($r=0{\cdot}486$; F-*test* = 4·96). *The 95 per cent confidence limits for the slope of the regression line and the 95 per cent confidence bands for the true mean of y are shown:* $y=0{\cdot}089x+109$; $r^2=0{\cdot}226$

Postoperative haematological findings

A complete response was achieved within the first month after surgery in 55 (89 per cent) patients. The mean postoperative platelet counts, haemoglobin levels and leukocyte counts are reported in *Table 1*. Forty-three of 49 patients with thrombocytopenia achieved complete remission after splenectomy, with a statistically significant increase ($P<0{\cdot}0001$) in platelet count (*Figures 1* and *2*). The significance was the same for the patients with platelet counts $<50\times10^9$/l. A statistically significant relationship was established between spleen weight and postoperative rise in platelet counts (*Figure 3*). No correlation was found between response and level of bone marrow megakaryocytes. Twelve of the 16 patients with anaemia had complete remission after splenectomy with a statistically significant increase in haemoglobin ($P<0{\cdot}001$ for CLL patients and $P<0{\cdot}05$ for NHL patients; *Figures 1* and *2*). No correlation was found between spleen weight and postoperative rise in haemoglobin. The effect of splenectomy on white cell count varied considerably from one patient to another in the CLL group. No statistical difference was noted between preoperative and postoperative count. There was a statistically significant increase for the entire NHL group and for the six patients with white cell counts $<3\times10^9$/l ($P<0{\cdot}001$; *Figure 2*). There was no relationship between spleen weight and reversal of leukopenia. There was no significant difference between preoperative and postoperative bone marrow films.

Seven of the ten patients (eight CLL and two NHL) with bicytopenia had a complete remission after splenectomy. Three of the five NHL patients with tricytopenia achieved correction of the three hematological abnormalities. One failed to correct thrombocytopenia and the other failed to correct anemia and white cell count.

Subsequent clinical course and survival

A continuing complete response was sustained in 39 (72 per cent) of the 54 responders (one postoperative death), with a median follow-up of 26 months (range 3–96 months).

Eighteen of 28 CLL patients with continuing complete response received chemotherapy and/or corticosteroids for an elevated white cell count and/or progression of nodal disease. Eight died, three of unrelated causes, with a median survival after splenectomy of 28 months (range 21–69 months). Ten patients had no postoperative treatment. A transient, greater than 50 per cent regression in palpable adenopathy was observed in five of these ten patients. Twenty patients are still alive in remission with a median survival of 38·5 months after surgery (range 3–89 months).

Nine of 11 NHL patients who had continuing complete response after splenectomy resumed full doses of chemotherapy, one with autologous bone marrow transplantation. In two cases radiotherapy was employed in addition to chemotherapy to treat massive nodal disease. Two patients had no postoperative treatment. Four of these 11 patients died of progressive disease with a median survival of 39 months after splenectomy (range 3–96 months) and seven are still alive in remission with a median survival of 7 months after splenectomy (range 3–25 months).

Of the five patients (all with CLL) who had partial response to splenectomy, one died after operation and four achieved complete remission with subsequent chemotherapy. Two of these patients are alive and well 30 and 61 months after splenectomy respectively and two died during the follow-up period, one with relapse into thrombopenia at 7 months and the other with end stage leukaemia at 69 months.

Of the 62 splenectomized patients, seven (11 per cent) did not respond and 15 (24 per cent) relapsed after surgery. The seven (three CLL and four NHL) with no response failed to respond to subsequent medical treatment. Five of these patients died of progressive disease with a median survival of 4 months (range 2–8 months). Two are alive but with a short follow-up of 3 and 4 months respectively. The 15 patients (12 CLL and three NHL) who relapsed after splenectomy received medical palliation. Only two (with CLL) are alive at the time of writing, 7 and 14 months after relapse and 30 and 31 months, respectively, after splenectomy. Thirteen patients died with a median survival of 6 months after relapse (range 1–30 months), and a median survival of 18 months after splenectomy (range 8–67 months). The cumulative risk of failure and relapse after splenectomy is shown in *Figure 4*. *Table 3* shows the clinical characteristics of the 22 patients who failed to respond or relapsed after splenectomy compared with those of the 40 patients who had a continuing complete response. Lower average preoperative and postoperative platelet counts ($P<0{\cdot}007$ and $P<0{\cdot}001$, respectively), lower rise in platelets ($P<0{\cdot}004$), lower average spleen weight ($P<0{\cdot}052$), and higher incidence of preoperative drug therapy ($P<0{\cdot}044$), were

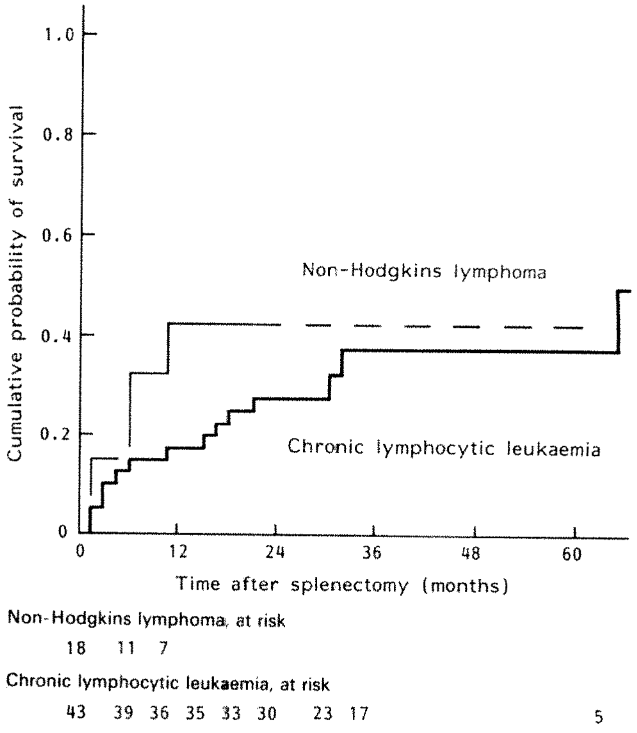

Figure 4 *The cumulative risk of failure of splenectomy and relapse into cytopenia after splenectomy for chronic lymphocytic lymphoma and non-Hodgkin's lymphoma. Incomplete failures or relapses (i.e. anaemia or thrombocytopenia or leukopenia) for patients who had two or three haematological abnormalities were taken into account*

Table 3 *Clinical data for 40 patients with continuing complete response and 22 patients with failure of splenectomy or relapse into cytopenia after splenectomy*

	Continuing complete response ($n=40$)*	Failure/relapse ($n=22$)†	t	P
Age (years)	60(12)	61(10)	0·52	0·612‡
Interval diagnosis–splenectomy (months)	38(39)	33(30)	0·49	0·633‡
Spleen weight (g)	1740(922)	1300(637)	1·96	0·052‡
Preoperative haemoglobin level (g/dl)	11·3(1·7)	10·6(1·6)	1·47	0·143‡
Postoperative haemoglobin level (g/dl)	12·5(1·4)	12·1(1·5)	0·84	0·593‡
Rise in haemoglobin (g/dl)	1·2(1·6)	1·5(2·3)	0·68	0·504‡
Preoperative platelet count ($\times 10^9$/l)	85(27)	60(41)	2·80	0·007‡
Postoperative platelet count ($\times 10^9$/l)	377(153)	233(150)	3·53	0·001‡
Rise in platelets ($\times 10^9$/l)	293(156)	173(136)	2·98	0·004‡
Sex (male/female)	23/17	12/10		0·965§
Interval diagnosis–splenectomy: <12 months/>12 months	16/24	9/13		0·840§
Chemotherapy before surgery/no treatment	21/19	18/4		0·044§

Values are mean(s.d.). * The data for the patient who died after operation were taken into account for the immediate response; excluding these data did not change any significance; † failures: three thrombocytopenia, four anaemia; relapses: seven thrombocytopenia, one anaemia, seven thromobocytopenia and anaemia; ‡ unpaired Student's t test; § χ^2 with continuity correction

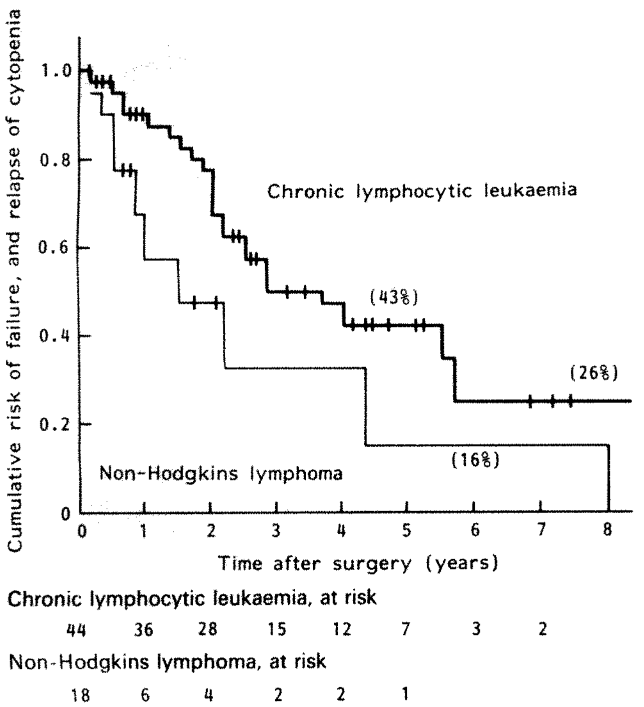

Figure 5 *The probability of survival plotted from the date of splenectomy for 44 splenectomized patients with chronic lymphocytic leukaemia, one postoperative death and three deaths unrelated to leukaemia are included, and 18 splenectomized patients with non-Hodgkin's lymphoma*

significant factors for the patients who failed to respond or who relapsed. In the subgroup of NHL patients, a lower average preoperative haemoglobin level ($P<0·02$) and a higher incidence of high grade NHL ($P<0·036$) were the only two significant factors related to failure or relapse. For the entire group of 62 patients, preoperative and postoperative platelet counts were the only two variables selected by stepwise regression analysis with a significant correlation ($P<0·05$ and $P<0·01$, respectively). On the other hand, bone marrow failure did not preclude a continuing complete response after splenectomy. Infections occurred with higher incidence during the follow-up of patients with failure or relapse than in patients with continuing complete response, but this difference was not statistically significant. There were no cases of fulminant postsplenectomy septicaemia induced by pneumococci or other polysaccharide bearing micro-organisms.

The 5-year CLL actuarial survival plotted from the date of splenectomy was 43 per cent and was flat after 6 years at 26 per cent (*Figure 5*). There was a significant difference in the 5-year survival rate between the 28 patients (one postoperative death) who had continuing complete response and the 15 patients who failed to respond or relapsed after splenectomy ($P<0·01$ at 60 months and $P<0·001$ at 67 months respectively). There was no significant difference in the 5-year actuarial survival rate between the CLL patients with nodular or diffuse splenic infiltration, nor was there a significant difference in survival rate between patients splenectomized less than 12 months after the diagnosis of CLL and the 32 patients splenectomized later in the course of their disease. The 5-year actuarial survival rates for these two groups of patients were 51 per cent and 42 per cent respectively. The 6-year actuarial survival rates were 17 per cent and 42 per cent respectively.

The 5-year NHL actuarial survival plotted from the date of the splenectomy was 16 per cent (*Figure 5*). There was a significant difference in the 5-year survival rate between the 11 patients who had continuing complete response and the seven patients who failed to respond or relapsed after splenectomy ($P<0·01$). There was also a significant difference in the 5-year survival rate between the seven patients with NHL of high grade malignancy (0 per cent at 26 months) and the 11 patients with NHL of intermediate or low grade malignancy ($P<0·05$). However, only one survivor of the latter group had a follow-up of 5 years.

Discussion

The operative mortality rate (1·6 per cent) and morbidity rate (29 per cent) in this study can be considered as satisfactory when compared with other recent series[7–11,15,27–33]. There is no question that salvage splenectomy performed on very ill patients carries a high risk of mortality and morbidity. The underlying disease and its stage have a major effect on postoperative course[10,11,14,15,19,20,28–33]. In the majority of recent series of elective splenectomy for haematological malignancies, the mortality rate did not exceed 10 per cent and was often zero[7,8,10]. The morbidity rate was about 15–35 per cent[7–11,16,19,27–33]. These results support the acceptability of the risk of splenectomy in selected patients with lymphoproliferative disorders. The only death in the present series was related to pulmonary embolism. Thromboembolic complications seem to be highly correlated with the underlying disease[20,29,33,34] and a 10 per cent rate of such complications has been reported in patients with hypersplenism, especially those with NHL[33]. No substantial increase in the incidence of thromboembolic complications has been detected in patients with thrombocytosis[30,34]. Fever of unknown origin has been reported as a frequent postoperative complication (more than 15 per cent) in splenectomized patients, particularly those with lymphoproliferative disease[30].

Overwhelming postsplenectomy infection is a subject of concern. All patients in this study received penicillin prophylaxis and pneumococcal vaccine, but there has been no published proof of benefit from long-term oral penicillin in adult patients[29], and patients with lymphoproliferative disorders have been reported to respond less well to vaccination[35]. Nevertheless, overwhelming postsplenectomy infection is rare in adult patients, even if the risk is present many years after splenectomy[9,12,29,36,37].

Reversal of cytopenia after splenectomy was satisfactory. The response rate was 89 per cent in the first month after surgery. A continuing complete response was sustained in 72 per cent of the initial responders with a median follow-up of 26 months. Three factors could have biased this uncontrolled study. First, the selection of patients submitted to splenectomy with respect to their general condition. Second, the number of really severe cases of thrombocytopenia, which occurred more frequently in advanced disease with life threatening symptoms. A lower average pre- and postoperative platelet count emerges as a significant factor in non-responders or relapsing patients in this and other series[14,19]. Third, the exclusion of autoimmune cytopenia. Although long term remission after splenectomy has been reported in patients not responding to steroids[11–14], the relapse rate is high and Coombs' positive patients are often poor or transient responders[9,11–15]. However, we feel that splenectomy in such patients is a different problem from splenectomy for hypersplenism.

The status of the underlying disease is probably the most important factor in determining haematological response[10,12,19]. Previous reports have emphasized the role of splenectomy in the early stage of disease in both CLL[7,12] and NHL[19,21,22]. Failure and relapse after splenectomy have been reported to be most probably due to very enlarged spleens with severe thrombocytopenia, a condition that is more frequent in advanced diseases. However, massive splenomegaly may be present in the early stage of disease and does not then preclude a satisfactory response to splenectomy[7–10]. In this series the reversal of cytopenia was not related to the interval between diagnosis and splenectomy, but a significant relationship was established between spleen weight and postoperative rise in platelet count[38].

Preoperative tests of erythrocyte and platelet survival and sequestration were used infrequently. These tests have commonly failed to predict response to splenectomy for lymphoma[7,8,13]. Thus, patients were splenectomized for presumed secondary hypersplenism, a condition for which splenectomy remains the only means of confidently determining the contribution of the spleen[6–8]. A major point of contention is whether or not bone marrow failure due to involvement with disease and previous treatment is an obstacle to the correction of cytopenia. In this series bone marrow failure did not preclude a response to splenectomy, but previous chemotherapy was significantly associated with failure to respond or relapse. Some authors recommend a current bone marrow examination before splenectomy, since hypersplenism is usually a presumed diagnosis. Adequate megakaryocytes and residual marrow function must be present if cytopenia is to be reversed[3,14,20,38–40]. However, response is frequently observed in the presence of bone marrow disease, especially when histological features are favourable and some normal marrow cells are present[2,5,7,8,12,17,19,41]. In this study, the NHL patients with high grade malignancy were at high risk of failure or relapse after splenectomy and there were no survivors after 26 months.

Splenectomy performed for massive symptomatic splenomegaly in the course of lymphoma improves the quality of life. The survival benefit for patients with hypersplenic complications is more debatable as splenectomy is only a part of the overall treatment[39,42], except for prolymphocytic leukaemia (one patient in this series) which responds poorly to chemotherapy and may be controlled by splenectomy[7,10,43]. However, the response to splenectomy appears to have some predictive significance regarding survival. Patients who fail to respond or relapse generally show a rapid progression of disease[7,8,12,13,17–22,29,38,41,44,45]. The deteriorating course of patients who fail to correct thrombopenia has been reported to be more rapid than those who fail to correct anaemia or leukopenia[19]. The correction of blood cell counts may allow the commencement or resumption of full dose chemotherapy, and a better tolerance and improvement in response to chemotherapy after splenectomy has been noted[7,8,13,19,29,45–47]. Splenectomy may also permit some patients to have no further immediate treatment[7,8]. It has also been suggested that the spleen is a major site for the production of malignant cells and if this is so splenectomy must benefit the disease[7–9,12,41].

Splenic irradiation may be an alternative to splenectomy for bulk symptoms, tumour control and hypersplenism. A few reports have been published on the topic, and subsequent splenectomy has often been done in irradiated patients[8,19,48]. Irradiation has been used for patients considered too ill to undergo splenectomy. However, response is likely to be poor or transient[8,13].

In conclusion, splenectomy in lymphoproliferative diseases such as CLL and NHL may be a worthwhile palliative procedure. The present results, based on a relatively large series of patients, suggest that splenectomy may be done successfully in spite of bone marrow failure, may enable the patient to start or resume full dose chemotherapy, may allow some patients to have no further immediate treatment, and may possibly improve survival for patients who obtain a complete and continuing response.

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Prediction of mortality by logistic regression analysis in patients with postoperative enterocutaneous fistulae

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The contrasting results of treatment of patients with postoperative enterocutaneous fistulae reflect the heterogeneity of the disease and depend on the patient's condition and the characteristics of the fistulae. For this reason, the use of a prognostic index, which enables such patients to be classified according to their risk of death, could be useful. In this study we propose a prognostic index based on a logistic regression analysis, obtained by using two (APACHE II score and serum albumin concentration) of the eight risk factors that have been retrospectively analysed in a series of 70 patients with postoperative enterocutaneous fistulae treated in our surgical department since 1981. The logistic regression equation indicates that patients with a probability of dying of less than 0·35 have a good prognosis, with a sensitivity of 90 per cent, a specificity of 90 per cent, a negative predictive value of 79 per cent, a positive predictive value of 96 per cent and an accuracy of 90 per cent. The predictive performance of the index has also been evaluated in a group of 17 patients studied prospectively, and this confirms the sensitivity and specificity of the model. This postoperative enterocutaneous fistulae index could be a helpful tool in clinical trials and surgical audit.

Keywords: Postoperative fistulae, prognostic index

To date, most of the papers dealing with postoperative enterocutaneous fistulae merely describe the number of cases treated and their outcome, reporting mortality rates ranging from 5 per cent to more than 30 per cent[1–3]. Although many local and general risk factors have been identified, a reliable prognostic evaluation of patients with postoperative enterocutaneous fistulae is still lacking.

Several prognostic classifications of patients with postoperative enterocutaneous fistulae have been proposed[4–7], mainly based on the number of risk factors present or on the characteristics of the fistula but, so far, no attempt has been made to use multiple regression analysis to identify the independent variables associated with poor outcome. The aim of this study was to develop a prognostic index by means of a logistic regression analysis which may be used in the management of patients with postoperative enterocutaneous fistulae and for their classification in clinical trials.

Patients and methods

The clinical records of 70 consecutive patients with postoperative enterocutaneous fistulae, treated in our surgical department over the 6 years from 1981 to 1986, were reviewed in order to identify the risk factors that correlate with the mortality rate and to determine an index of severity. There were 41 men and 29 women aged between 19 and 79 years (median age 53·5 years). A further group of 17 new patients (median age 57 years, range 28–74 years; 13 men and four women) with postoperative fistulae were evaluated prospectively during the past 20 months in order to confirm the predictive ability of the model.

Definitions

The eight potential risk factors considered were defined as follows:

1. Sepsis; the presence of a septic focus with at least two of the following general signs: temperature >38°C, leucocytosis >12000 per mm^3, heart rate >110 per min, hyperventilation >24 per min. In order to measure the severity of the sepsis we adopted the APACHE II classification system and, following the Knaus approach[8], we assigned a different risk class with every five points of APACHE II score.

2. Hypoalbuminaemia; a level of serum albumin concentration <35 g/l[5,9–11]. For better management of the data, four classes of serum albumin concentration were also considered: class 0 (≥ 35 g/l), class 1 (30–34·9 g/l), class 2 (25–29·9 g/l), class 3 (<25 g/l).

3. High output; the loss of more than 500 ml secretion per day for a period longer than 3 days[7,12].

4. Site of the fistula; fistulae arising from the upper gastrointestinal tract (oesophagus, stomach, duodenum), pancreas and biliary tree, and those from the small and large intestine were considered separately[5,10].

5. Age; patients aged >60 years were considered to be at high risk.

6. Associated diseases; possible risk factors considered were the presence of acute and chronic renal failure, acute and chronic hepatitis or cirrhosis, heart diseases such as severe arrhythmia, infarction, unstable angina and myocardial insufficiency, immunosuppression due to radiotherapy or chemotherapy, steroids, acute and chronic pulmonary diseases with reduction in respiratory function, and insulin-dependent diabetes.

7. Cancer; the presence of a malignant tumour, regardless of its site and stage.

8. Local conditions unfavourable to spontaneous healing; these were distal obstruction, mucocutaneous continuity or epithelialization of the fistula tract, complete intestinal leakage, abscess along the fistula tract, bleeding from the fistula, fistula tract involved by the original disease (cancer or Crohn's disease), laparotomy wound dehiscence >20 cm^2, multiple fistulae and lateral duodenal fistulae[5,6,13].

Statistical methods

Different statistical analyses were performed according to the type of variables considered: a χ^2 test was used for cross tabulations based on qualitative variables and a Student's t test was used for quantitative variables. A Brand–Snedecor χ^2 test was performed in order to verify the linear regression component of the χ^2 test for the proportion of survivors, a proportion that increased or decreased according to the

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Table 1 *Original diseases and types of fistula in 70 patients*

	Oesophageal	Gastric	Terminal duodenal	Lateral duodenal	Pancreatic	Biliary	Jejunal	Ileal	Colonic
Oesophageal achalasia		○							
Gastric cancer	○	○	● ○		●				
Duodenal ulcer			○ ○ ○ ● ● ○	○					
Biliary tract disease			○	○ ○ ○ ○		○ ○ ○	●		
Hepatic hydatidosis				● ○		○ ○			
Pancreatic cancer					● ○ ○ ○	● ○		● ●	
Chronic pancreatitis				●	○ ○ ○ ● ●				
Diverticulitis									○
Laparocœle								○	
Colorectal cancer				●			○	○ ○ ○ ○ ● ● ○ ○	○ ○ ○
Crohn's disease								●	
Uterine cancer								● ○	
Uterine fibromyoma									○
Bladder cancer								○	○
Renal lithiasis								○	
Lymphoma								●	
Appendicitis							●	● ○	○ ○
Iatrogenic lesions							○		○

○, Survivors (49 patients); ●, non-survivors (21 patients)

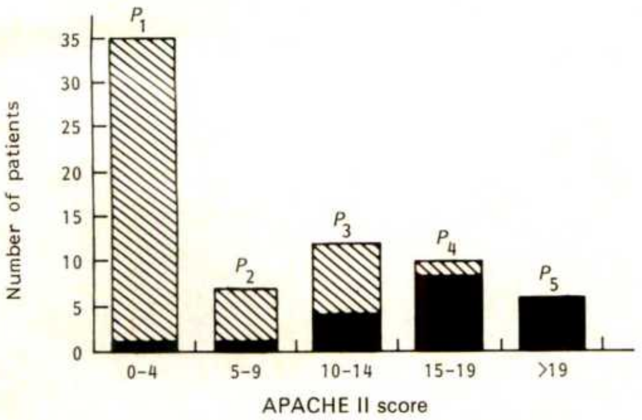

Figure 1 *Patient outcome according to APACHE II classes:* ▨, *survivors;* ■, *non-survivors. Probability of survival:* $P_1=0{\cdot}971$, $P_2=0{\cdot}857$, $P_3=0{\cdot}667$, $P_4=0{\cdot}1$, $P_5=0$

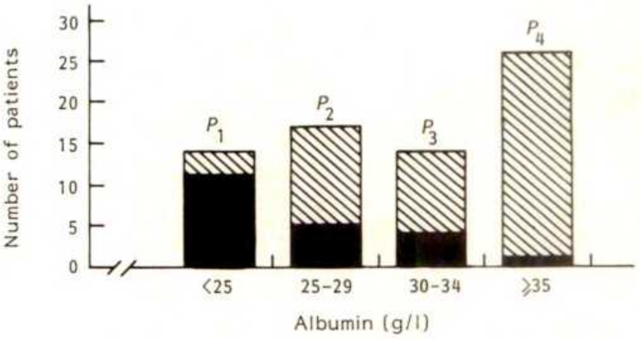

Figure 2 *Patient outcome according to albumin levels:* ▨, *survivors;* ■, *non-survivors. Probability of survival:* $P_1=0{\cdot}214$, $P_2=0{\cdot}706$, $P_3=0{\cdot}692$, $P_4=0{\cdot}962$

risk classes of the variables such as albumin and APACHE II. A logistic regression analysis was then applied[14] taking into account those variables that carried a high prognostic significance when examined by univariate analysis. The estimation of the parameters related to the independent variables in the logistic equation was determined via a maximum-likelihood method.

Furthermore, χ^2 and Wald tests measuring the linear hypothesis with respect to the information matrix obtained from the likelihood calculations were carried out in order to determine the statistical significance of the parameters in the logistic regression equation.

Finally, a test to evaluate the sensitivity and specificity of the statistical model with respect to the observed data was performed on the retrospective and prospective groups of patients.

Results

The type of fistula and the original disease diagnosed and treated are reported in *Table 1*. The overall mortality rate was 30 per cent. Sepsis was present in 28 patients (40 per cent), 15 of whom died (54 per cent mortality rate) compared with six of the 42 patients without sepsis (14 per cent). The difference in percentage between the sepsis and non-sepsis group was statistically significant ($\chi^2=12{\cdot}35$, $P<0{\cdot}001$).

The distribution of death according to the APACHE II classes is shown in *Figure 1*. The risk of death increased with APACHE II class ranking: the total χ^2 ($\chi^2_3=44{\cdot}3$, $P<0{\cdot}001$) and its linear component ($\chi^2=41{\cdot}1$, $P<0{\cdot}001$) showed that the differences were statistically significant.

The mean value of serum albumin was 25·7 g/l in non-survivors whereas it was 33·3 g/l in survivors ($t=5{\cdot}047$, $P<0{\cdot}001$). Survival rate decreased with decreasing albumin levels (*Figure 2*). The total χ^2 and the linear regression component showed that the differences were also statistically significant in this case ($\chi^2_3=24{\cdot}2$, $P<0{\cdot}001$; $\chi^2=20{\cdot}91$, $P<0{\cdot}001$). The presence of high output was also found to be significantly related to the risk of death ($\chi^2=12{\cdot}35$, $P<0{\cdot}001$). Local unfavourable factors, the site of the fistula, associated diseases, the presence of cancer and age over 60 years were not statistically associated with outcome.

A first logistic regression analysis was carried out using the three variables (APACHE score, high output and serum albumin) which were statistically related to outcome after univariate analysis. However, the regression coefficient of the high output showed no significant correlation ($\chi^2=0{\cdot}11$, $P=0{\cdot}74$). A second logistical regression equation was therefore used with APACHE II score and serum albumin as the only two prognostic factors. The logistic equation obtained was:

$$\ln[P/(1-P)]=4{\cdot}87-0{\cdot}769\ \text{albumin}-1{\cdot}667\ \text{APACHE II}$$

where P is the probability of survival and albumin and APACHE values are expressed by classes. The results of the statistical analysis are reported in *Table 2* and the relationship between individual values of P and survival is shown in *Figure 3*. It is clear from the Equation that the risk of death increased directly with the increase in the albumin and APACHE II class.

A classification matrix, showing the distribution of the patients according to the observed outcome and that predicted by the model, was derived from the values of the estimate of individual survival rates obtained from the Equation using a decision criterion of 0·65 (*Table 3* and *Figure 3*). This value was found to have a sensitivity of 90 per cent, a specificity of 90 per cent, a positive predictive value of 96 per cent, a negative predictive value of 79 per cent and an accuracy of 90 per cent in distinguishing survivors from non-survivors.

In the new group of 17 patients evaluated prospectively, five deaths occurred. There was one oesophageal fistula, one gastric fistula, two lateral and two terminal duodenal fistulae, two pancreatic fistulae, four small bowel fistulae and five colonic fistulae. Using the same decision criterion used in the first group of patients, a sensitivity of 100 per cent, a specificity of 80 per cent, a positive predictive value of 92 per cent, a negative predictive value of 100 per cent and an accuracy of 94 per cent were found.

Discussion

Owing to the heterogeneous nature of postoperative enterocutaneous fistulae, the evaluation of treatment adopted or comparison of results obtained in different hospitals would require an enormous amount of detailed information on both the characteristics of the fistulae and the general condition of each patient. A method of overcoming this problem could be the identification of risk factors influencing the mortality rate in order to establish a prognostic index to be used as a common base in evaluation.

During the past few years, many conditions have been found to be individually associated with the risk of dying in patients with postoperative enterocutaneous fistulae, including local factors (high output, multiple fistulae) and general factors (age, sepsis, malnutrition, associated diseases)[15–17]. However, only the association between each of these factors and a poor outcome has been investigated and, although this association was almost always statistically significant, it would not be correct statistical practice to use this information to predict outcome[18].

Greater accuracy in predicting survival rate has been obtained by using a combination of factors to identify postoperative fistulae classes with different risks of mortality. For example, Sitges-Serra *et al.*[7] identified four different groups of fistulae, according to site and output, with different mortality rates. Fujita and co-workers[5] proposed four degrees of postoperative fistulae depending on whether or not concomitant abscesses or peritonitis were present, with a mortality rate ranging from zero to 65 per cent even when patients were treated with total parenteral nutrition. Furthermore, Levy and co-workers[6] described a classification system for patients with

Table 2 *Statistical results of the logistic regression equation*

Effect	d.f.	Estimate	s.d.	χ^2	P
Intercept	1	4·877	1·185	16·95	0·0001
Albumin	1	−0·769	0·413	3·47	0·0623
APACHE II	1	−1·667	0·447	13·85	0·0002

Table 3 *Comparison of observed outcome and outcome as predicted by logistic regression analysis*

	Predicted		
	Alive	Dead	Total
Retrospective group of 70 patients			
Observed			
Alive	44	5	49
Dead	2	19	21
Total	46	24	70
Prospective group of 17 patients			
Observed			
Alive	12	0	12
Dead	1	4	5
Total	13	4	17

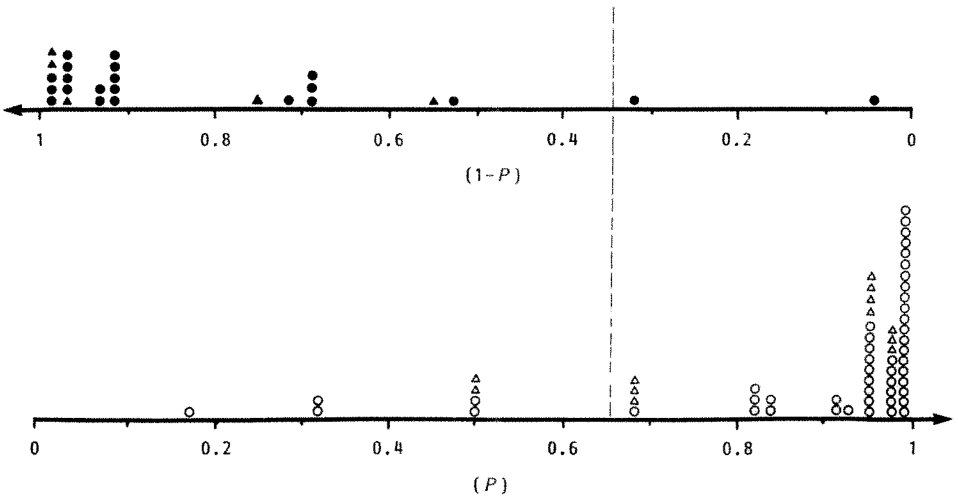

Figure 3 *Distribution of the patients according to the results of the logistic regression equation, where* P *is the probability of survival;* ○, *survivors;* ●, *non-survivors in the retrospective group* (n=*21*); △, *survivors;* ▲, *non-survivors in the prospective group* (n=*5*). *The vertical dotted line denotes a decision criterion of 0·65*

small bowel fistulae opening through an abdominal wall defect; they identified 12 risk factors and four classes of increasing risk of death (from zero to 86 per cent mortality rate) according to whether zero, one or two, three or four, five or more risk factors were simultaneously present.

A more complete and generally applicable prognostic classification system (the fistula prognostic score) has recently been developed and validated prospectively in our surgical department by scoring four risk factors (sepsis, serum albumin, high output and locally unfavourable conditions)[4]. However, the use of a logistic regression model has enabled us to reduce the number of prognostic variables influencing the outcome. The APACHE II system, which is an accurate index of the severity of the illness, and serum albumin, which is the simplest and most commonly used index of malnutrition, are the only independent variables that strongly influence the prognosis in such patients. Furthermore, most of the prognostic factors identified by others[2,3,19] can be included in the APACHE II score, or may have relevance in determining the APACHE II score, so that this variable alone can indicate the relative importance of these risk factors fairly accurately.

The results of our univariate analysis confirm previous reports showing that the presence of high output was significantly correlated to the outcome[3,6,7]. However, this variable did not improve the prediction of outcome when included in the logistic regression model. This could be because high output is often associated with loss of albumin through the fistulae and with severe metabolic imbalance detected by the APACHE II system. For this reason it cannot be considered an independent variable and was therefore not included in the final regression equation. According to the model developed, patients with a probability of death of less than 0·35 have a good prognosis.

Early detection of low albumin levels and metabolic imbalance has therefore a direct therapeutic implication, suggesting that every effort must be made to treat sepsis and to correct malnutrition as soon as possible in the management of patients with postoperative enterocutaneous fistulae.

In agreement to Wassons *et al.*[18] we believe that 'prediction rules are a form of health care technology, and they should be studied with the same care as new drugs or devices', emphasizing, however, that information drawn from such predictive models should be handled carefully. As with all predictive indices, this model cannot be used in clinical practice as a prognostic index for individual patients. It is not 'a crystal ball to predict the future of our patients'[20]. Nevertheless it can be a helpful tool in classifying patients with different risks of death.

Although a larger series of patients with postoperative enterocutaneous fistulae would be required to validate this predictive model further, we think that this approach would make it easier to compare different types of management of homogeneous groups and to identify patients at high risk of mortality in need of a more vigorous surgical and medical treatment.

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Demonstration of blood flow patterns in human soft tissue sarcomas using ^{99m}Tc-labelled hexamethyl propyleneamineoxime

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Blood flow patterns have been studied in 28 patients with soft tissue sarcoma (29 tumours) using ^{99m}Tc-labelled hexamethyl propyleneamineoxime with planar views of the tumour-bearing region. Tumour:background ratios ranged from 1·13 to 6·60 (mean 2·74) and maximum:minimum tumour ratios (between peripheries and centres of tumours) ranged from 1·34 to 32·0 (mean 4·70). In eight of 29 tumours (seven of which were involving the trunk) the tumour could not be identified. This study demonstrates that the blood supply to soft tissue sarcomas is generally greater than that to adjacent normal tissues and that tumour centres are relatively underperfused compared with the tumour periphery. In this heterogeneous series there was no clear-cut relationship between blood flow and histological grade or type.

Keywords: Soft tissue sarcoma, tumour blood flow, isotope imaging, ^{99m}Tc-HMPAO

Soft tissue sarcomas are uncommon tumours whose prognosis depends principally on stage at presentation (which includes histological grade) although outcome, particularly at the primary site, is also dependent on treatment undertaken. Treatment options include a combination of surgery, radiotherapy and chemotherapy, with particular attention to local control.

Blood flow through tumours may be an important factor in determining natural history, influencing metabolism and growth, and in determining response to treatment. Tumours that are poorly perfused will be poorly oxygenated and access to chemotherapy may be limited. Tumours in other sites, for example primary lung tumours, have been shown to be less well perfused in central regions, and central perfusion decreases with increasing tumour size[1]. Demonstration of poorly perfused regions within solid tumours indicates the need for further investigation of drug penetration and has implications for the timing of radiotherapy. The use of vasoactive agents to increase tumour blood flow and to enhance responsiveness might be considered.

A suitable technique for the measurement of tumour blood flow in humans should be relatively non-invasive and reproducible, and should allow some form of quantification. Imaging after intravenous administration of ^{99m}Tc-labelled hexamethyl propyleneamineoxime (^{99m}Tc-HMPAO) permits demonstration of regional differences in perfusion both between tumours and normal tissues and within tumours.

^{99m}Tc-HMPAO is a lipophilic compound with high first-pass extraction[2] whose retention has been shown to be proportional to blood flow in the brain[3,4] and in tumours[5]. Investigations of tumour perfusion with ^{99m}Tc-HMPAO and single photon emission computed tomography (a rotating γ camera technique with subsequent computerized reconstruction) have been undertaken in patients with tumours in a variety of sites[6] (including one patient with a liposarcoma), brain tumours[7] and lung tumours[1]. These studies show a range of values of uptake into the area occupied by the tumour compared with contralateral normal tissue with minimal abnormality of perfusion in adjacent normal tissues.

We present our findings in a series of patients with soft tissue sarcomas whose blood flow patterns have been investigated with ^{99m}Tc-HMPAO.

Patients and methods

Twenty-eight patients with a definitive diagnosis of soft tissue sarcoma admitted to the Academic Surgical Unit of the Royal Marsden Hospital were studied. Initial staging procedures included chest radiography and computed tomography and magnetic resonance imaging of the primary site. Angiography was not performed. After initial assessment and before admission to the Surgical Unit, nine patients had undergone a course of radiotherapy and eight had received chemotherapy; four patients had received both. The study was approved by the Royal Marsden Hospital Ethics Committee and informed consent was obtained from each patient.

Mean age was 51·7 years (range 19–83 years); 19 patients were men and nine were women. There were 29 tumours in a variety of sites (*Table 1*); in one patient there were two tumours, one in each calf. Definitive histology was obtained at operation in all patients (*Table 2*).

Planar images were obtained 20 min after the intravenous injection of 500–750 MBq ^{99m}Tc-HMPAO (Ceretec, Amersham International, Amersham, UK) using a General Electric Starport γ camera (IGE Medical Systems Ltd., Slough, UK). Tumour:background ratios were obtained by comparing the counts seen in a region of interest within the tumour periphery and in a region of interest within an area of adjacent normal tissue. A similar technique was employed to obtain maximum:minimum ratios between tumour periphery and tumour centre.

The relationship between tumour:background ratios and tumour maximum:minimum ratios and previous treatment, histological grade and the presence of metastases was investigated by two-tailed t test; that between tumour:background and maximum:minimum ratios and tumour size by linear regression analysis; and that between positive tumour demonstration and site by Fisher's exact test. Tumour volume was determined from measurements of the pathological specimen. In instances where tumour size had been recorded in only two dimensions, the third dimension was taken to be the mean of the first two and volume was calculated according to the formula:

$$\text{Tumour volume} = \frac{4\pi}{3} \times \frac{(x \times y \times z)}{8}$$

where x, y and z represent tumour dimensions.

Results

After imaging with ^{99m}Tc-HMPAO, activity within eight of the 29 tumours could not be distinguished from that in adjacent normal tissues. Seven of 13 tumours involving the trunk but only one of 16 tumours affecting the limbs could not be

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identified in this way (Fisher's exact test, $P = 0{\cdot}007$). In the remaining 21 tumours greater activity was seen compared with that in normal tissues with a mean tumour:background ratio of 2·74 (range 1·13–6·60; *Figure 1*). In 19 of 21 tumours central activity was less than peripheral activity with a mean maximum:minimum tumour ratio of 4·70 (range 1·34–32·0; *Figure 2*). *Table 3* shows tumour:background ratios and tumour maximum:minimum ratios according to previous treatment. Ratios were unaffected by prior radiotherapy or chemotherapy when considered separately or together.

Figures 3 and *4* show examples of the increased uptake seen in a malignant peripheral nerve sheath tumour (low grade) of the right thigh in a 27-year-old man and in a high-grade synovial sarcoma of the calf in a 47-year-old man. This latter example shows the presence of a large tumour in the right calf together with a smaller (previously unsuspected) tumour in the left calf. *Figure 5* shows a similar pattern of uptake in an intermediate-grade myxoid liposarcoma overlying the angle of the left scapula in a 64-year-old man, and in *Figure 6* there is uptake in a high-grade synovial sarcoma of the left thigh in a 35-year-old man. All these examples show the characteristic pattern of greater uptake in the tumour periphery than the tumour centre with areas of inhomogeneous uptake distributed throughout the tumour.

There was no correlation between either tumour:background ratios or tumour maximum:minimum ratios and tumour size ($r = -0{\cdot}12$ and $r = 0{\cdot}03$ respectively). No significant association was seen between tumour uptake of $^{99\text{m}}$Tc-HMPAO and either histological type or grade or the presence of metastases at diagnosis.

Table 1 *Tumour site in 28 patients with soft tissue sarcoma*

Tumour site	Total number ($n = 29$)	Number not identified on scan
Limb		
Thigh	9	1
Lower leg	6	–
Forearm	1	–
Trunk		
Scapula	3	1
Chest wall	1	–
Epigastrium	1	1
Retroperitoneum	4	3
Pelvis	1	1
Buttock	2	1
Hindquarter stump	1	–

Table 2 *Histological results in 28 patients with soft tissue sarcoma (29 tumours)*

	Histological grade			
Histological type	High	Intermediate	Low	Total
Malignant fibrous histiocytoma	6	2	–	8
Liposarcoma				
Myxoid	2	1	2	8
Sclerosing	–	–	1	
Pleomorphic	1	–	–	
NOS	–	–	1	
Synovial sarcoma	2	–	–	2
Malignant peripheral nerve sheath tumour	1	–	2	3
Epithelioid sarcoma	1	–	–	1
Chondrosarcoma (soft tissue)	–	1	2	3
Leiomyosarcoma	1	–	1	2
Rhabdomyosarcoma	1	–	–	1
Soft tissue sarcoma (NOS)	1	–	–	1

NOS, not otherwise specified

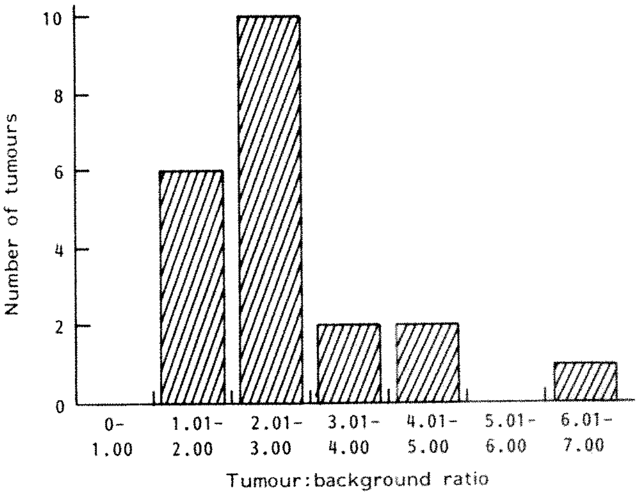

Figure 1 *Distribution of tumour:background ratios*

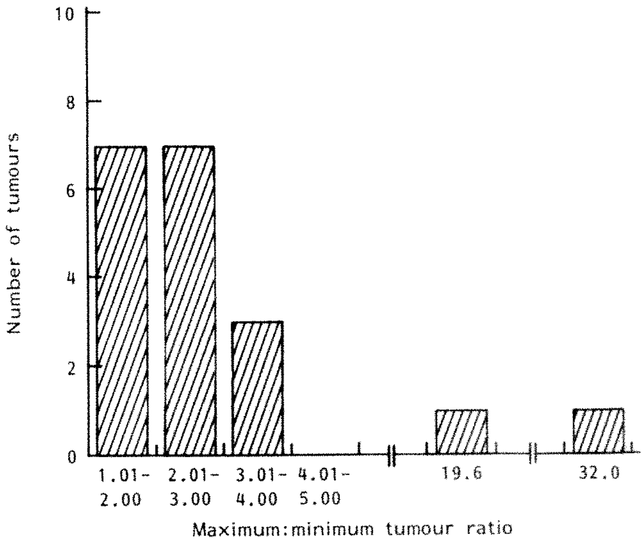

Figure 2 *Distribution of tumour maximum:minimum ratios*

Table 3 *Tumour:background ratios and tumour maximum:minimum ratios* versus *previous treatment*

Previous treatment	Total number	Number assessable	Tumour:background*	Number assessable	Maximum:minimum*
None	16	10	3·04(1·55)	9	4·09(5·87)
Any	13	11	2·48(1·02)	10	5·32(9·41)
Radiotherapy alone	5	5	2·62(1·27)	5	8·43(13·21)
Chemotherapy alone	4	4	2·45(0·98)	4	2·05(0·89)
Radiotherapy and chemotherapy	4	2	2·19	1	2·82

* Values are mean(s.d.)

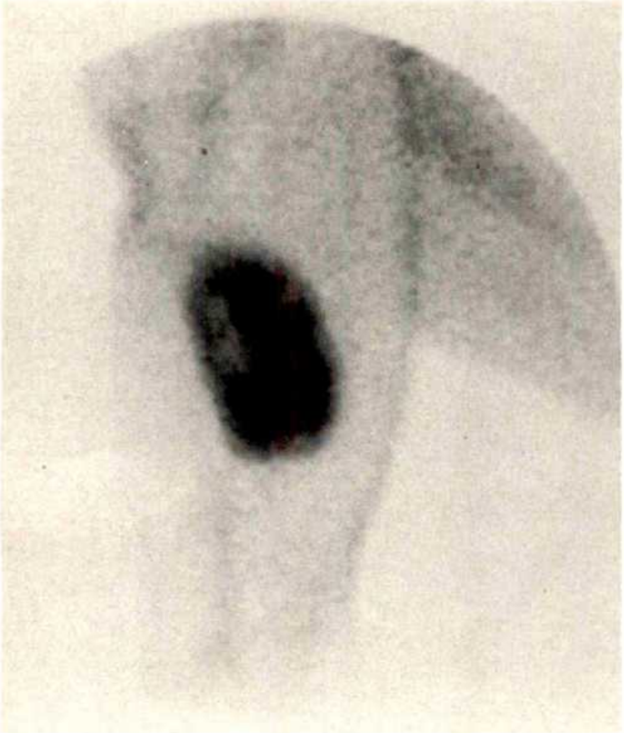

Figure 3 *Malignant peripheral nerve sheath tumour (low grade) of the right thigh in a 27-year-old man*

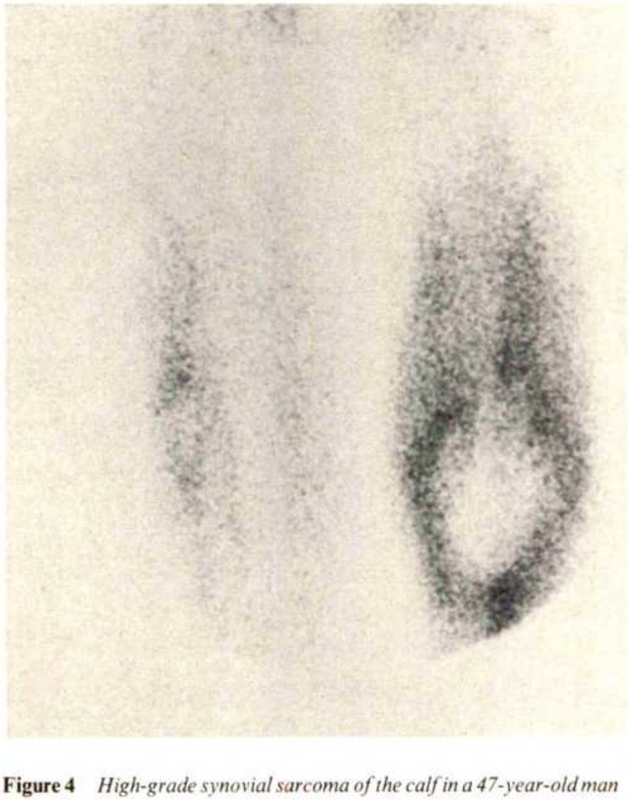

Figure 4 *High-grade synovial sarcoma of the calf in a 47-year-old man*

Discussion

This study demonstrates high uptake of ^{99m}Tc-HMPAO in soft tissue sarcomas with a large differential between peripheral and central uptake. A proportion of soft tissue sarcomas appears to be resistant to irradiation and chemotherapy, and although a component of this resistance is due to intrinsic radioresistance or chemoresistance, the presence of large poorly perfused areas within tumours may contribute to treatment failure. The development of a technique which demonstrates regional differences in tumour blood supply provides the basis for further studies into drug access and the relationship between tumour oxygenation and treatment outcome.

In this series, tumours of the trunk were less reliably identified on planar views. It is unlikely that their pattern of perfusion is substantially different from that of limb tumours but rather that trunk tumours would have been obscured by equal or greater activity in deep or superficial tissues.

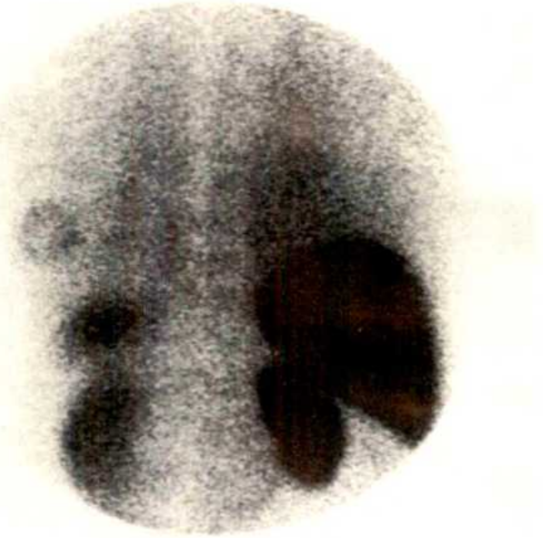

Figure 5 *Intermediate-grade myxoid liposarcoma overlying the left scapula in a 64-year-old man*

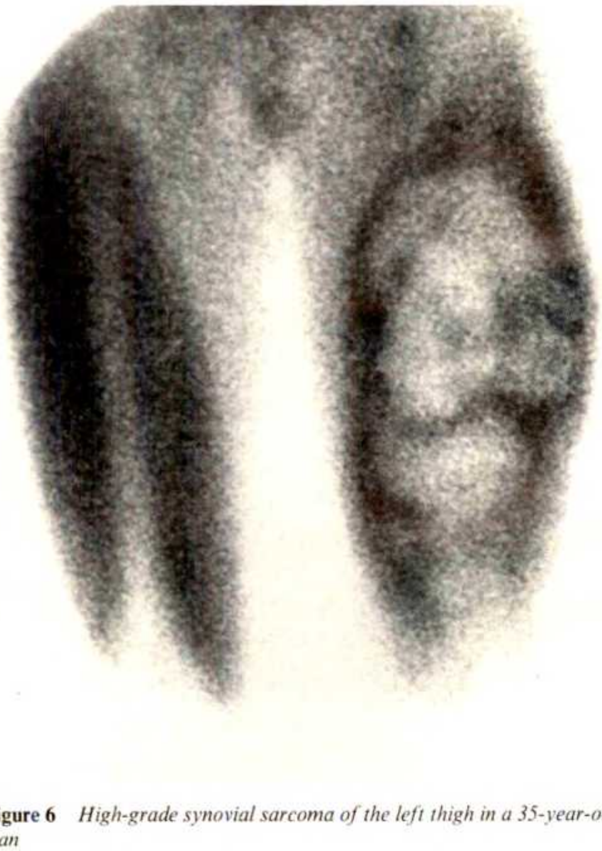

Figure 6 *High-grade synovial sarcoma of the left thigh in a 35-year-old man*

Alternatively trunk tumours may less often possess the characteristic ring of increased uptake which allows easy discrimination from surrounding tissues. The use of single photon emission computed tomography may prove to be of value in deep-seated tumours. The absence of correlation between tumour:background ratios and tumour size is in contrast with a study of primary lung tumours[1] in which lower tumour:background ratios were found in larger tumours.

A number of clinical studies have investigated the ability of radiopharmaceuticals to demonstrate the presence or extent of soft tissue sarcomas, for example the uptake of gallium[8] or ^{99m}Tc-diphosphonate[9] by malignant fibrous histiocytoma, ^{201}thallium by haemangioendothelioma[10], ^{99m}Tc-bleomycin and ^{99m}Tc(V)-DMSA (dimercaptosuccinic acid) by liposarcoma[11] or ^{111}indium-labelled antimyosin antibodies by leiomyosarcoma and rhabdomyosarcoma[12]. Whilst such imaging procedures may be of value in staging and in the early detection of recurrence, demonstration of the physiological state of the tumour requires the use of a radiopharmaceutical agent whose uptake is directly related to metabolism or perfusion (e.g. ^{99m}Tc-HMPAO). Such radiopharmaceuticals have an advantage over angiography which can demonstrate only larger vessels and cannot provide direct information concerning the capillary network from which tumour cells derive oxygen and nutrients. Arteriovenous shunts may be seen with angiography but as these enable blood to bypass rather than to perfuse tumour cells, information about tumour metabolism is lacking.

While a number of metabolic studies have been performed in tumours in other sites, only the study by Kern *et al.*[13] has investigated metabolic activity using ^{18}fluorine-labelled 2-fluoro-2-deoxy-D-glucose in soft tissue sarcomas. In three soft tissue sarcomas the glucose utilization rate was increased relative to normal tissue to a degree that paralleled the histological grading. In any series of soft tissue sarcomas such relationships are complicated by the large number of histological subtypes.

In summary, soft tissue sarcomas are generally better perfused than surrounding normal tissues but contain large areas of poor perfusion. This technique is of value in the demonstration of blood flow within tumours and offers opportunities to examine more closely the relationship between tumour biology and treatment outcome.

Acknowledgements

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Hypertensive anal cushions as a cause of the high anal canal pressures in patients with haemorrhoids

Anorectal manometry and electrophysiology studies were conducted in 25 men with non-prolapsing haemorrhoids, ten men with prolapsing haemorrhoids, and 20 age-matched normal men. Mean(s.e.m.) minimum basal pressures were significantly higher in patients with non-prolapsing haemorrhoids than in normals (61(5) versus *43(7) cmH_2O; $P<0.05$) or patients with prolapsing haemorrhoids (55(4) cmH_2O; $P<0.05$). There were no significant differences in maximum basal pressures and maximum squeeze pressures. During rectal distension, all normal subjects showed relaxation in all anal channels. However, 92 per cent of patients with non-prolapsing haemorrhoids and 40 per cent of patients with prolapsing haemorrhoids showed no relaxation in the outer anal channels, even when relaxation occurred in the inner anal channels; internal sphincter electrical slow waves were suppressed and the integrated electrical activity of the external sphincter had returned to predistension values. Maximum residual anal pressures during balloon distension were significantly higher in patients with non-prolapsing haemorrhoids than normals (75(7)* versus *45(7) cmH_2O; $P<0.01$), or patients with prolapsing haemorrhoids (53(3) cmH_2O; $P<0.05$). When subjects increased intra-abdominal pressure rectal pressure was significantly higher in patients with non-prolapsing haemorrhoids than in normal subjects (157(10)* versus *105(15) cmH_2O; $P<0.05$), but not in patients with prolapsing haemorrhoids (126(14) cmH_2O). Resting anal cushion pressures in patients with non-prolapsing or prolapsing haemorrhoids were much higher than normal capillary or venous pressure and significantly higher than those recorded in normals (median 35, 35* versus *10 cmH_2O; $P<0.0001$). Pressures recorded during coughing (60, 60* versus *30 cmH_2O) and straining (78, 80* versus *55 cmH_2O) were also significantly higher ($P<0.0001$) in patients than in normals. Pressures after straining were higher than those recorded before (38* versus *29 cmH_2O; $P<0.05$) in 60 per cent of patients but no normal subjects and took 18–36 s to return to baseline. This study suggests that the abnormally high pressures in the anal canal in patients with haemorrhoids may be related to an increased vascular pressure in the anal cushions.*

Keywords: Anal cushion, haemorrhoids, anus, rectum, electromyography

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Patients with haemorrhoids often complain of obstructed defaecation[1,2]. The stool often requires vigorous straining and even sometimes digitation to remove it. Most but not all manometric studies have shown an abnormally high resting anal pressure in patients with haemorrhoids. It is generally assumed that the abnormally high anal pressures are caused by an increased tonic activity in the internal anal sphincter[1,3] and the external anal sphincter[4]; such activity may hinder defaecation and be responsible for expanding the anal cushions by impairing venous drainage[5]. Forcible dilatation of the anal canal to disrupt the muscle fibres reduces sphincter pressures to normal[6,7], but pressures are also reduced by removal of the anal cushions[8], suggesting perhaps that the pressure in the vascular spaces may contribute to high anal pressure in patients with haemorrhoids.

The anal cushions resemble erectile tissue in that they contain large blood spaces fed by arterioles[9]. In normal subjects they may help to preserve continence by forming an expansile anal seal[10]. When hypertrophied, however, they could plug the anus, impair defaecation and cause straining. This study has used combined electrophysiological and manometric techniques to investigate the existence and the source of the high anal pressures in patients with haemorrhoids.

Patients and methods

Subjects included 25 men, aged 31–65, mean = 49(3) years, with non-prolapsing first degree haemorrhoids. Ten of these patients complained of the need to strain excessively in order to defaecate, four of incomplete evacuation after defaecation, and 18 complained of bleeding after defaecation. Ten men aged 30–74, mean 53(5) years with prolapsing haemorrhoids were also studied; two complained of the need to strain to defaecate and one of incomplete evacuation. All patients with prolapsing haemorrhoids complained of bleeding after defaecation.

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The patients were examined by an independent observer either on the day of the test or within 2 weeks of the test. At anoscopic examination, all three anal cushions appeared enlarged. As the patients strained the anal cushions bulged into the anal lumen and increased in size. Sigmoidoscopy and barium enema ruled out the presence of any colonic disease.

Twenty men, aged 21–63, mean = 41(6) years, $P > 0{\cdot}05$, who had no history of anorectal disease and no abnormality at anoscopy, served as a control group.

All subjects gave their informed consent for the tests to be performed and the study was approved by the Ethical Subcommittee of the Sheffield Area Health Authority.

Combined manometry and electromyography

All subjects underwent dynamic tests of anorectal function using simultaneous multiport manometry and anal sphincter electromyography. No bowel preparation was used prior to the test, but subjects were allowed to empty their rectum before the test if they felt the need to do so.

Anorectal pressures and sphincter electromyography were recorded with the patients in the left lateral position and the hips flexed to 90°. A seven lumen polyvinyl catheter, which had an external diameter of 4 mm and terminated in a small latex balloon (Durex Dry, LPC Products Ltd., London, UK), was inserted into the anal canal. When in the correct position, manometric side holes were situated 0·5, 1, 1·5, 2, 2·5 and 4·5 cm from the anal margin and the lower pole of the balloon was situated 8 cm from the anal verge. Each manometric channel was perfused with water at a constant rate of 0·4 ml/min by means of a low compliance system containing a reservoir and capillary tubing (Mui, PIP2, Mississauga, Ontario, Canada), and pressures were recorded by transducers (Statham, 23ID, Oxnard, California, USA), situated in each infusion line. The output of each transducer was recorded continuously on an eight-channel recorder (Hewlett-Packard, 7758A, Waltham, Massachusetts, USA).

A bipolar wire electrode consisting of two trimel coated wires (diameter = 0·025 mm)[11,12] was used to perform electromyography of the external anal sphincter and internal anal sphincter, and was inserted without anaesthetic into the groove between the superficial external and the internal sphincters. The free ends of the wires were bared and attached to an amplifier (Differential type 21C01 URO-DISA, Skovlunde, Denmark), frequency range 1 Hz–10 kHz, which was connected via an integrator (A.C. to R.M.S. convertor, Analog Devices AD536, Surrey, UK) to the chart recorder. Both raw and integrated electromyography signals (170 ms time constant) were displayed on the chart recorder. The activity of the internal anal sphincter was represented on the raw electromyography record as a regular oscillation, which occurred at a frequency of between 6 and 20 per minute and increased in amplitude as the activity of the muscle increased[13], and occasionally as a low amplitude oscillation on the integrated record. The activity of the external anal sphincter appeared on the integrated record as an elevation above the baseline and on the raw electromyography record as frequent, irregular spikes that increasd in amplitude and frequency as the activity of the muscle increased. The maximum integrated electrical activity of the external anal sphincter recorded during rectal distension and straining was expressed as a percentage of that recorded during maximum conscious contraction of the sphincter.

Direct measurement of pressures in the anal cushions

With the subjects in the left lateral position, pressures in the anal cushions of ten normal subjects and 20 patients with haemorrhoids (15 non-prolapsing, five prolapsing) were measured using a spinal needle (25 G) perfused with 5 per cent glucose at the rate of 3 ml/h and connected to a pressure transducer. A slit proctoscope was inserted into the anal canal, and rotated so that the anal cushion protruded into the lumen when the obturator was removed. In this way the vascular pressure could be recorded without any contribution from the anal sphincters. Drainage of blood from the anal cushion is parallel to the axis of the anus, and is unlikely to be impeded using a slit proctoscope[9].

Protocol

Resting sphincter pressures and electromyograph activity were measured for about 30 min, during which the pressures gradually fell to reach a steady baseline. The pressures at the beginning of this period and after the pressure had been at a steady state for at least 15 min were recorded as the maximum and minimum basal pressures, respectively. Ultraslow waves were identified according to established definitions[6]. The subject was then instructed to contract the external sphincter as strongly as possible and maintain the contraction for at least 20 s. This action was repeated on two further occasions with an interval of at least 1 min between each contraction. After a 5 min resting period, the rectal balloon was serially inflated with increasing volumes of air (10, 20, 40, 60 and 100 ml). Each inflation was maintained for 1 min, the balloon was then deflated and a gap of at least 1 min was allowed before the next inflation. Subjects were asked to report if they perceived the distension and grade the sensation as a feeling of gas (wind), a feeling of stool in the rectum, a desire to defaecate, an urgent desire to defaecate and pain.

After a rest of at least 10 min, subjects were instructed to increase the intra-abdominal pressures by straining as if to defaecate for 30 s. This was repeated on two occasions separated by a rest period of 1 min.

After a further 10 min rest, the pressures in each anal cushion were measured in turn. Resting pressures were recorded for 1 min, then the subjects were asked to give a vigorous cough and to strain as if to defaecate for 5 s. These manoeuvres were repeated three times separated by gaps of at least 12 s.

Pressures were judged to be recorded from the anal cushions when they showed a regular respiratory oscillation and an increase on coughing and on straining, but otherwise remained quite stable. Occasionally there was bleeding from the puncture site. If this occurred during measurement, the pressure reduced and the reading was rejected. If the needle did not penetrate the cushion, the pressure demonstrated a ramp like increase indicating the outflow was obstructed.

Statistical analysis

All data were examined primarily by using a normal probability plot technique[14]. This predicted that the data obtained with the anal manometry probe were normally distributed. An analysis of variance was used to evaluate the differences between normal subjects and patients. Data obtained from direct pressure measurement in anal cushions and sensory data were assessed by the Mann–Whitney *U* test. The χ^2 test was used to determine the differences between the percentage of the patients and normals who showed a given phenomenon.

Results

Basal and sphincter squeeze pressures

None of the patients experienced discomfort with the probe *in situ*. After insertion of the catheter, the basal pressure slowly fell to a stable low level over 15 min. The minimum basal pressures at all anal ports were significantly higher ($P < 0{\cdot}05$) in patients with non-prolapsing haemorrhoids than in normal subjects and patients with prolapsing haemorrhoids, and in patients with prolapsing haemorrhoids than in normal subjects ($P < 0{\cdot}05$) (*Table 1*). The maximum basal and maximum squeeze pressures were not significantly different among groups (*Table 1*). Ultraslow waves were observed in the resting recording from the seven patients (28 per cent) with non-prolapsing haemorrhoids and three patients (30 per cent) with prolapsing haemorrhoids. Ultraslow waves were not seen in the control subjects ($P < 0{\cdot}05$).

Anorectal responses to rectal distension

Distension of the rectal balloon in all normal subjects caused reductions in pressures in all ports, increasing in amplitude and duration as the distending volume increased, such that the lowest sphincter pressures were attained at volumes of 60 ml. These anal relaxations were associated with increases in rectal pressure and transient increases in the electrical activity of external anal sphincter and suppression of the electrical slow wave activity of the internal anal sphincter (*Figure 1*). On deflating the balloon, the anal pressure showed rebound increases to values that exceeded the pre-inflation pressure. The amplitude of this rebound was greater, the larger was the distending volume, and it was associated with increases in the amplitude of the internal anal sphincter slow waves (*Figure 1*). Ninety-two per cent of patients with non-prolapsing haemorrhoids and 40 per cent of patients with prolapsing haemorrhoids ($P < 0{\cdot}001$) failed to show any reduction in pressure in the outermost anal channels during rectal distension ($P < 0{\cdot}01$ in both groups compared with normal subjects) (*Figure 1*). Twenty-four per cent of patients with non-prolapsing haemorrhoids ($P < 0{\cdot}02$ compared with normal subjects) and 10 per cent of patients with prolapsing haemorrhoids showed

Table 1 *Anorectal pressures and electrical activity of the external anal sphincter during resting, during rectal distension and during straining in normal subjects and patients with non-prolapsing and prolapsing haemorrhoids*

	Normal subjects ($n=20$)	(Patients Non-prolapsing ($n=25$)	 Prolapsing ($n=10$)
Basal pressure (cmH_2O)			
Maximum	102(5)	108(4)	104(4)
Minimum	43(7)†	61(5)	55(4)†‡
Squeeze pressure (cmH_2O)	272(15)	264(11)	265(18)
Pressure at rectal distension with 100 ml of air (cmH_2O)			
Pre-inflation	90(5)	98(6)	85(10)
Residual	45(7)†	75(7)	53(5)†
Rebound	125(11)	126(12)	115(14)
Pressure during straining (cmH_2O)			
Rectal	105(15)†	157(10)	126(14)†
Anal	204(27)	222(17)	191(20)
Electrical activity during rectal distension of 100 ml (%)*	58(7)	59(8)	58(8)
Electrical activity during straining (%)*	72(8)	61(10)	65(10)

Values are mean(s.e.m.); * results expressed as a percentage of the activity recorded are an equivalent time during maximum contraction of the sphincter; † significantly different from patients with non-prolapsing haemorrhoids, $P<0.05$; ‡ significantly different from normal subjects, $P<0.05$

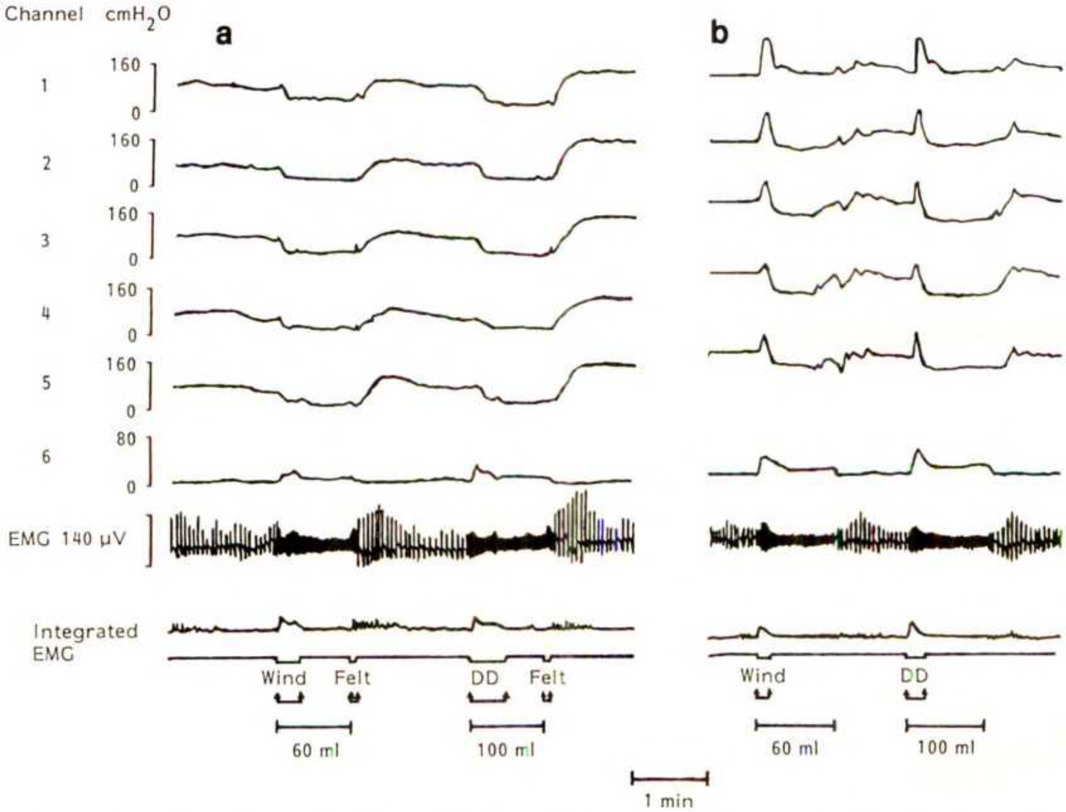

Figure 1 *Recordings of anorectal pressure and the electrical activity of the external anal sphincter and internal anal sphincter before, during and after inflation of a rectal balloon with 60 and 100 ml of air in a normal subject* (**a**) *and in a patient with non-prolapsing haemorrhoids* (**b**). *Channels 1 to 6 represent ports situated 0·5, 1·0, 1·5, 2·0, 2·5 and 4·5 cm from the anal margin. Note that rectal distension in normal subjects induces a relaxation in sphincter pressure associated with abolition of the electrical oscillations, produced by internal anal sphincter activity, and an increase in the electrical activity of the external anal sphincter, whereas deflation produces a rebound increase in pressure which is associated with a marked increase in the slow wave oscillations. In the patient with haemorrhoids, there was no anal relaxation in the outermost channels during the balloon distension, though the electrical activities of the external anal sphincter and internal anal sphincter appeared normal. DD, desire to defaecate; EMG, electromyography*

no reduction in pressure at any site in the anal canal. The differences between preinflation and residual pressures at maximum rectal distension were much smaller in patients with non-prolapsing haemorrhoids compared with normal subjects or patients with prolapsing haemorrhoids (20(4) *versus* 51(8) and 37(7); $P<0.05$). This result was caused by a higher residual anal pressure in the patients with non-prolapsing haemorrhoids (*Table 1*, $P<0.05$), although the residual pressure recorded from patients with prolapsing haemorrhoids lay between the normal subjects and patients with non-prolapsing haemorrhoids. The corresponding preinflation and rebound anal pressures in the three groups were not significantly different (*Table 1*).

Table 2 *Comparison of rectal sensitivity in normal subjects and patients with non-prolapsing and prolapsing haemorrhoids during rectal distension (ml)*

	Normal subjects ($n=20$)	Patients Non-prolapsing ($n=25$)	 Prolapsing ($n=10$)
Perception	13(2)	14(1)	13(2)
Wind	32(5)	39(5)	29(5)
Desire to defaecate	76(7)	68(5)	58(8)

Values are mean(s.e.m.)

Table 3 *Pressure measurement in the anal cushions in normal subjects and patients with non-prolapsing and prolapsing haemorrhoids*

	Normal subjects ($n=10$)	Patients Non-prolapsing ($n=15$)	 Prolapsing ($n=5$)
Basal pressure (cmH_2O)			
Median	10*	35	35
Range	0–25	20–80	10–70
Pressure during coughing (cmH_2O)			
Median	30*	60	60
Range	10–50	30–80	30–85
Pressure during straining (cmH_2O)			
Median	55*	78	80
Range	40–80	45–90	45–85

* Significantly different from patients with non-prolapsing or prolapsing haemorrhoids

The failure of the outer sphincter to relax in response to rectal distension and the high residual pressures in patients with non-prolapsing haemorrhoids occurred despite the fact that rectal distension inhibited internal anal sphincter slow wave activity in all patients and relaxations were observed in the inner anal channels in 68 per cent of patients. Although rectal distension increased external anal sphincter activity, this was only transient, returning rapidly to preinflation values within 24 s in 84 per cent of subjects, and there were no significant differences in external anal sphincter electrical responses to rectal distension between patients and normal controls (*Table 1*). Thus in most patients with non-prolapsing haemorrhoids the maintenance of a high pressure in the outer anal channels did not appear to be related to sphincter contraction.

The volumes at which patients with haemorrhoids perceived the rectal balloon, or experienced a feeling of wind, a desire to defaecate and the maximum intolerable discomfort were not significantly different from those recorded in normal subjects (*Table 2*). None of the subjects or patients experienced pain during rectal distension up to 100 ml.

Anorectal changes during increases in intra-abdominal pressure

On increasing intra-abdominal pressure by straining down, normal subjects and patients with haemorrhoids showed increased electrical activity in the external anal sphincter and the pressures in the more distal anal canal rose to levels that were consistently above the rectal pressure. Patients with non-prolapsing haemorrhoids, however, had significantly higher ($P<0{\cdot}05$) pressures in the rectum (*Table 1*) during straining compared with normals and patients with prolapsing haemorrhoids. The pressures in the outermost anal ports and the electrical activity of the external anal sphincter were not significantly different from normal subjects (*Table 1*).

Pressure measurements in the anal cushions

There were no significant differences between the pressures measured in the non-prolapsing haemorrhoids or the prolapsing haemorrhoids (*Table 3*). The basal pressures in the anal cushions in either group of patients were significantly higher ($P<0{\cdot}0001$) than in normal subjects (*Table 3, Figure 2*). During a cough, the pressure increased immediately and the peak pressure recorded during coughing was significantly higher ($P<0{\cdot}0001$) in patients than normals (*Table 3, Figure 2*). The pressure recorded during straining for 5 s was also significantly higher ($P<0{\cdot}0001$) in patients than in normals (*Table 3, Figure 2*) and the haemorrhoids became visibly swollen. In 12 (nine non-prolapsing and three prolapsing) patients (60 per cent) the pressure remained above the pressure recorded before straining (median = 38 *versus* 29 cmH_2O; $P<0{\cdot}05$) even when the straining effort had ceased, returning to baseline between 18 and 36 s later (median = 24 s) (*Figure 2*). The pressure always returned promptly to the baseline in normal subjects (*Figure 2*). There were no significant differences between pressures recorded in each of the three anal cushions in each group.

Discussion

Many patients with haemorrhoids have difficulty in defaecating[1,2]. Forty per cent of patients with non-prolapsing haemorrhoids in our study reported that they strained during defaecation and 16 per cent felt that evacuation was incomplete. When they strained, patients produced higher pressures in the rectum than age and sex matched normal subjects. These observations suggest that patients with non-prolapsing haemorrhoids have an increased anal resistance to passage of faeces.

The technique of combined multiport anorectal manometry and electromyography allowed us to assess the contribution made by the different components of the sphincter in patients with non-prolapsing haemorrhoids. Our results confirmed that resting sphincter pressures in a carefully selected group of patients with non-prolapsing haemorrhoids were abnormally high, though maximum basal pressures, recorded shortly after insertion of the probe, and maximum squeeze pressures were similar to those measured in normal subjects.

Distension of the rectum caused a reduction in sphincter pressure in the innermost channels in most patients with non-prolapsing haemorrhoids, but the pressure in the outer

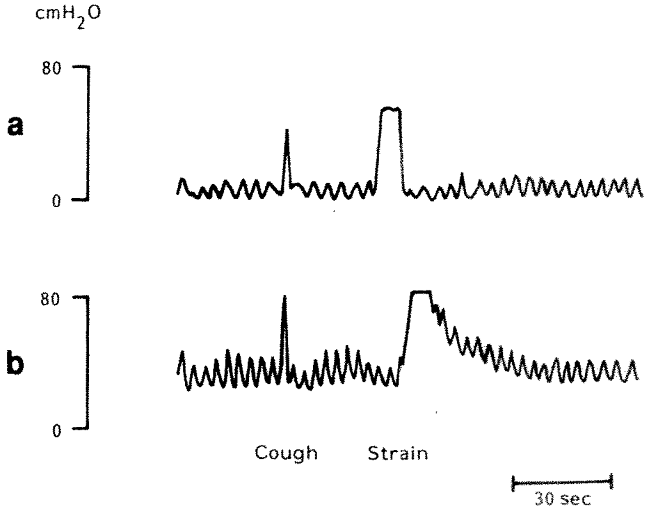

Figure 2 *The pressure recorded in anal cushion in a normal subject* (**a**) *and in a patient with non-prolapsing haemorrhoids* (**b**) *under resting condition, during coughing and before, during and after straining. Note that: (1) the pressure profile showed respiratory oscillations under resting conditions; (2) the pressure recorded during coughing was higher in patients than in normal subjects; (3) pre-straining and straining pressures were higher in patients than in normal subjects; (4) the pressure promptly returned to pre-straining level in normal subjects, but remained elevated in patients with non-prolapsing haemorrhoids*

channels was usually maintained at the high basal values. In 24 per cent of patients with non-prolapsing haemorrhoids pressures were maintained at a high level throughout the sphincter. It is unlikely that maintenance of this high pressure barrier was related to persistent activity in the internal anal sphincter, since the inner aspect of the sphincter exhibited a relaxation of normal amplitude in most subjects and the electromyography showed abolition of the normal regular oscillation of the internal sphincter. Relaxation of the internal anal sphincter was not masked by compensatory contraction of the external anal sphincter. Although the external sphincter showed the expected increases in activity immediately after rectal distension, this was transient and in most cases had declined to pre-inflation values within 24 s of balloon distension. By exclusion, therefore, these results suggest that the mechanism responsible for the high resting and residual pressures in the outer anal canal could be an abnormally high vascular pressure in the anal cushions. The observation that patients whose haemorrhoids were prolapsed had minimum basal and residual pressures that were significantly lower than patients with non-prolapsing haemorrhoids would support that conclusion.

These pressures within the anal cushions have not been measured previously, but the resemblance of the anal cushions to erectile tissue[9,10,15] suggested that they would lie between arterial and venous pressures. We measured the pressure within the anal cushion directly via a perfused needle connected to a pressure transducer. In order to do this, it was necessary to abolish the contribution of sphincter muscle contraction to intravascular pressure, by using a proctoscope that had a slit through which the anal cushion could protrude. If we had not used the slit proctoscope, the pressure within the vascular space would have been identical to that in the sphincter lumen. Drainage of venous blood from the anal cushion is parallel to the axis of the anus[9], and is unlikely to be impeded using a slit proctoscope. Our results showed that the pressure within the anal cushions in normal subjects was similar to normal venous or capillary pressure, and showed normal respiratory oscillations and responses to increases in intra-abdominal pressure. The pressures within the hypertrophied anal cushions of patients with non-prolapsing and prolapsing haemorrhoids were not significantly different, but were much higher than in normal subjects and increased to very high levels when the patients strained as if to defaecate. If the haemorrhoids could prolapse this would make little difference to anal pressures but if the haemorrhoids were unable to prolapse the anal pressures would be increased.

Although the basal pressure within the anal cushion was abnormally high, it was still lower than the pressure recorded in the resting sphincter, even when the electrical records indicated very little activity in the sphincter muscles. The most likely reason for this is that under normal circumstances the pressure in the resting sphincter is related to both the vascular pressure and the elasticity of the anal wall. If the anal wall is stretched by the proctoscope, then the elastic component is abolished and perhaps venous drainage from the anal cushion is facilitated. The possibility that a higher internal sphincter tone could impair venous return and account for the increased pressure in the haemorrhoid group seems unlikely since the indwelling proctoscope would usually relax the internal anal sphincter[16]. Also, if the venous drainage through the internal sphincter is impeded, the blood can drain through other penetrating vessels in the rectal wall[17]. The observation that only the residual and minimum basal pressures were abnormally high in patients with non-prolapsing haemorrhoids, whereas maximum squeeze and maximum basal pressure were normal, suggests that the vascular contribution is greatest when the sphincter muscles are relaxed, and that a strong contraction of the sphincter may squeeze the blood out of the anal cushions.

During defaecation, both internal and external sphincters normally relax to facilitate expulsion of the stool. Under conditions of sphincter relaxation, the presence of dilated anal cushions would create an anal resistance which patients could only overcome by increasing their intra-abdominal pressure. This may explain why straining is associated with higher rectal pressures in patients with non-prolapsing haemorrhoids than in normal subjects. The persistence of the high vascular pressure after straining might further impair the passage of the stool. It has been suggested that strenuous attempts to force a stool through a partially obstructed canal would produce an abnormal shearing force, which would not only impede venous drainage from the cushions, causing further engorgement, but also stretch and disrupt the connective tissue that supports the anal lining during defaecation, causing intermittent and then permanent prolapse of the anal cushions[9]. Once the haemorrhoids can prolapse, the pressure in the rectum reverses to nearly normal.

The possibility that the anal resistance in patients with haemorrhoids is related to the engorged haemorrhoids themselves and not to any concomitant increases in anal muscle tone reinforces the idea that the correct surgical approach is to reduce the vascular mass by injection, banding, electrocoagulation or excision. Internal sphincterotomy or forcible anal dilatation to weaken the sphincter muscle are only logical if the tone in that muscle is causing the engorgement of the cushions by obstructing venous return. There is no strong evidence for this; indeed, if, as we have previously argued, the anal cushions play an important role in preserving continence[10] then engorgement would take place when the sphincter is relaxed and not when it is contracted.

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Satisfying patients' needs for surgical information

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Patients facing operation need good information. This is implicit in informed consent but it is often lacking. A solution is a comprehensive set of leaflets covering 65 different general surgical operations. The leaflets describe the illness, operation, exact management regimen, some complications and outlook, in a deliberately simple style. Master copies are stored on a wordprocessor to allow unlimited expansion and updating. A retrospective survey of 200 patients showed that those receiving leaflets were significantly more satisfied with information (72 per cent overall) than those not receiving leaflets (42 per cent overall) ($P < 0.01$)*. This was especially apparent for information about postoperative progress, both in hospital (92 per cent* versus *52 per cent) and after discharge from hospital (88 per cent* versus *39 per cent). The system is effective, cheap and popular with patients and medical and nursing staff. The wordprocessor allows extensive modifications of the information to suit other surgeons' requirements.*

Keywords: Computer assisted instructions, information systems, patient education

Good information, well communicated to patients, is an essential part of surgical practice. It is fundamental to informed consent. Although it can improve the progress and even shorten the hospital stay of surgical patients[1], many have reported dissatisfaction with the amount of information given about hospital procedures[2,3].

The surgical team faces an understandably increasing desire for information from today's sophisticated patient[4,5]. At the same time, the complexities of the latest operations and surgical management become ever more difficult to explain to the lay person. Indeed, traditional verbal communication, one of the profession's weak points[6], is probably inadequate for modern requirements. The medicolegal aspects of providing satisfactory information are clear to all practitioners.

Information written to satisfy the most demanding patient facing the most complex operation should be effective in complementing the spoken word. Techniques for producing highly readable instructions are well established, though often ignored[7,8]. Such a large volume of information, covering many different operations, is ideally stored, easily updated, and rapidly printed by a computer with a wordprocessor. We report the use of such an information system in a general surgical practice.

Patients and methods

Over a period of 4 years, a set of information leaflets was built up covering 65 different general surgical operations encountered in a district general hospital. Each leaflet consisted of a description of an illness, an operation, preoperative care, recovery in hospital and after discharge from hospital, common complications and outlook. Comprehensibility was sought by avoiding, or at least explaining, technical jargon, by keeping sentences short, by avoiding polysyllables, by using personal pronouns, and by giving specific advice rather than vague generalizations[6,7]. Special versions were produced for parents of children undergoing surgery. Although the leaflets gave a guide to one type of surgical management, patients were warned in them that they were not comprehensive and that they might see some difference in their own management. Patients were encouraged verbally to ask questions and to comment on the content of the leaflets. Their comments and experience were used constantly to revise the information, so enhancing its relevance.

The data were stored as free text on a 720 kilobyte floppy disk of an Apricot F2® (Apricot Computers PLC, Birmingham, UK) computer with a Wordcraft® (Wordcraft International, Colchester, UK) wordprocessor for editing and updating. Photocopies were filed in the outpatient department, to be given to patients as they were offered operations. Other copies were available on the wards for emergency cases and in-hospital referrals. Sets of leaflets were sent to general practitioners to keep them informed about current surgical regimens.

From January 1987, a questionnaire was given to patients at their first follow-up visit to assess their reaction to the information given. Similar questionnaires were also given to two groups of control patients consisting of contemporary patients who had operations not covered by the leaflets, and earlier patients who had had operations before the leaflets came into use. Patients were asked how much information they felt they had received about different aspects of their surgery, and from what sources. This perceived information was scored by patients as 'none', 'too little', 'a little', 'average', 'a lot', or 'too much'.

The leaflets ranged from three pages of A4 paper for the simplest procedure, to seven pages for the most complex (oesophagectomy). The 65 leaflets covered 90 per cent of general surgical operations in the British United Provident Association's Schedule of Surgical Procedures. They occupied 320 pages (600 kilobytes) on the computer disk, leaving space on the disk for about ten more leaflets. However, overspill on to other disks is straightforward.

The readability of the leaflets was easier than that of the popular tabloid newspapers with a mean sentence length of 11 words, and with only 10 per cent of words having three or more syllables (Fog Index 8)[8]. Each leaflet contained information which would take at least 20 min to receive verbally, let alone learn or digest. Since each leaflet was so closely tailored to each operation, their issue to patients was supervised by medical staff to prevent the wrong leaflet being handed out.

After being given a leaflet to read through as often as he or she wished, the patient was invited to ask supplementary questions.

The survey was not randomized because the leaflets were being continuously modified and developed. Fifteen per cent of patients did not return the questionnaire, leaving 200 replies from 100 patients who had received leaflets and from 100 who had not. Only positive answers have been analysed (about 10 per cent of questions were not filled in). We judged a patient satisfied if he or she recorded receiving 'average' or 'a lot' of information. Dissatisfaction was recorded for 'a little', 'too little' or 'too much' information. Significance was evaluated by the rank Anova test.

Results

Table 1 shows that the groups were well matched for age and sex. The numbers of major and intermediate cases were skewed but this did not affect the results, because the satisfaction rates were almost identical in the three operation subgroups. The two control groups without leaflets have been combined to provide a

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Table 1 *Structure of patient group receiving leaflets compared with group not receiving leaflets*

	Leaflets	No leaflets
Age in years (s.d.)	50·4 (19·3)	52·8 (18·7)
Number of males	43	35
Number of females	57	65
Major operations	36	57
Intermediate operations	57	32
Minor operations	7	11

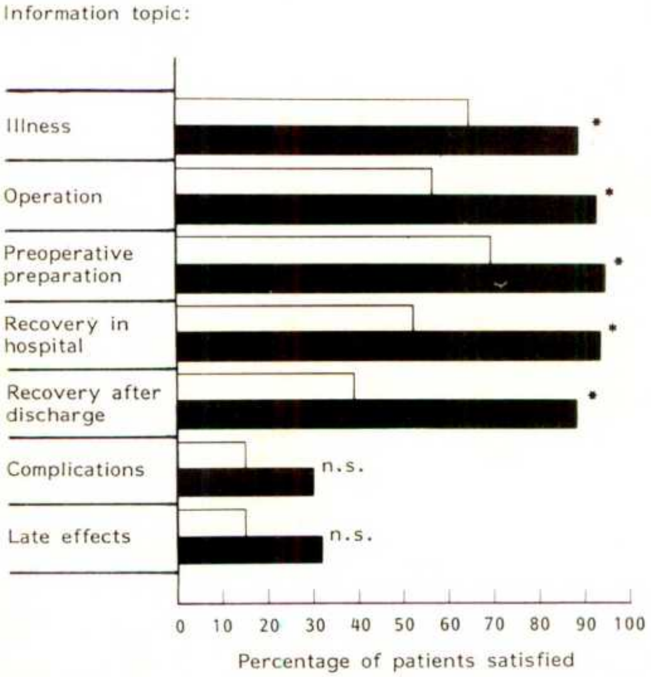

Figure 1 *Percentage satisfaction according to information topic among 100 patients receiving leaflets compared with 100 patients without leaflets.* □, *Non-leaflet group;* ■, *leaflet group;* * $P < 0{\cdot}01$; *n.s., not significant*

population comparable in size with that which received leaflets. Those treated before the leaflets were introduced were overall more satisfied than the contemporary leaflet non-receivers (52 per cent *versus* 37 per cent respectively). There was a significantly higher percentage of overall satisfied patients among those who had leaflets (72 per cent) than among those who did not receive leaflets (42 per cent) ($P < 0{\cdot}01$). *Figure 1* is a breakdown of the overall figures, showing low satisfaction generally with information about complications and about late effects, but showing high satisfaction among the leaflet receivers for all other aspects.

In the whole series, only two patients felt they had had 'too much' information. Both were in the group which received leaflets and both concerned complications. Leaflet receivers and non-receivers alike felt that they had obtained similar small amounts of satisfactory information from friends and relatives or that they already knew some information (*Figure 2*). General practitioners were seen as a source of satisfactory information by 57 per cent of patients with leaflets, compared with 45 per cent of patients without leaflets (n.s.). In hospital, however, patients with leaflets were significantly more satisfied than those without, not only with the written information but also with information from doctors and nurses.

Discussion

Patients grasp the essentials of even the most complex operations with impressive speed. As a rule they ask most enlightened supplementary questions. Also, patients are most grateful for details about such things as washing, stitches, lifting and time off work, which are not high priorities for the surgeon preoccupied with ensuring a successful operation.

In a busy outpatient clinic, the patient is relieved of the problem of remembering a mass of verbal information and the surgeon does not have to struggle to explain the basics of pathology and anatomy. At home the patient can study the leaflets with relatives and friends. Each leaflet was read an average of five times by the patient and others. On the ward, the patient can re-read the leaflet at will and can even plot progress along the planned surgical pathway using the leaflet as a guide. Some patients who have not received leaflets have complained of being deprived of information. Junior surgical staff have used the system for reference about management regimens and have been known to take whole sets of leaflets with them as they left for other posts. Nurses have used the leaflets as teaching aids as well as for their primary purpose.

Surgical colleagues in other hospitals have modified the data to provide information tailored exactly to their own regimens. Transfer of the data (using American Standard Code for Information Interchange (ASCII) files) to virtually any computer/wordprocessor combination is straightforward. These surgeons have needed to edit less than 5 per cent of the original data to suit their own preferences. Editing is simple and quick for any secretary with modest wordprocessing skills and merging the system into surgical audit software has been easy.

In our survey the satisfaction rate in the group which did not receive leaflets was as low as in most published series, confirming the view that traditional ways of communicating information are poor. The higher satisfaction rate in the group with leaflets, for all aspects of surgery including complications and late effects, is probably real, although a randomized prospective trial would be needed for absolute confirmation. The very high satisfaction for written information about recovery was gratifying, since it was suspected that this aspect was probably the least well covered by the spoken word.

The low satisfaction with written information about complications and late effects may have arisen because the leaflets were confined to the effects of the operations rather than the effects of the underlying diseases. There is room for improvement here and the topic is being investigated. The higher level of satisfaction with information from ward doctors and nurses recorded by the patients who received leaflets was an unexpected finding. It

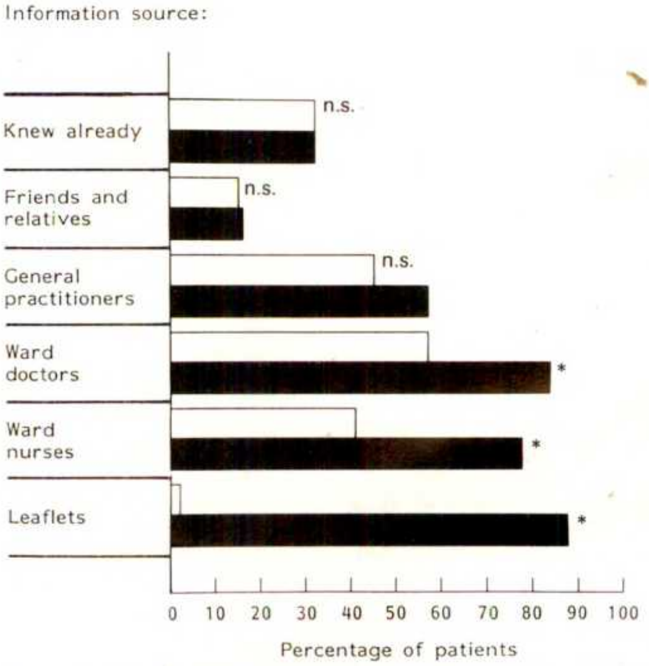

Figure 2 *Percentage satisfaction according to information source among 100 patients receiving leaflets compared with 100 patients without leaflets.* □, *Non-leaflet group;* ■, *leaflet group;* * $P < 0{\cdot}001$; *n.s., not significant*

may reflect the leaflets' invitation to patients to ask questions. It may mean that ward staff absorbed the data on the leaflets and were more able and willing to give responsible answers. It does show that the written word had unexpected secondary benefits on communication in surgery.

In the literature, written information for patients is 'of great validity but lacks experimental support'[9]. Caplan recommended written information for patients when the problem is repetitive, complex, multifaceted, or provokes many questions[10]. Fletcher stated that the written word is more likely than the spoken word to overcome forgetfulness and misunderstanding[11]. However, written instructions neither improved compliance for sperm counts after vasectomy nor reduced anxiety or improved satisfaction among parents of children undergoing heart surgery[12,13]. In contrast, Ley has demonstrated the positive value of written instructions in the treatment of obesity, but pointed out that a difficult leaflet is no better than no leaflet[14].

Alternative information systems are well known. Pamphlets and books are cheap and easy to obtain, but their advice is often rather too general, and some have a low readability. They can be difficult to update. Audiotapes have many of the advantages of computerized leaflets, but they are difficult to scan and search[15]. Videotapes are powerful communication tools, but require complicated equipment for presentation, are difficult to update, and are expensive. Specially trained communication staff are often ideal, but are even more expensive. A combination of methods together with personal interest from senior staff may ultimately give the best results. At present, however, the patient may be grateful for any information from whatever source[16].

Sellu described a computerized system using a database to generate information leaflets for common operations[17]. Despite a Fog Index of 12·4, which suggests that the information was getting difficult to read, 90 per cent of patients found the leaflets useful, though there were no controls. The database (dBase II, Human Dynamic Systems, California, USA) raises the cost of the equipment, but allows more sophisticated applications such as printing of personalized letters. With a similar investment, the wordprocessor system described in this paper easily adapts to do the same.

The relationship between patient satisfaction with, and understanding of, information is not clear cut. In one study 16 per cent of patients satisfied with information about their diagnoses recalled the wrong condition[18]. Kupst *et al.*[13] showed that satisfaction was related to a feeling of getting information, and was not related to being able to recall it. Villar and Hume[19] showed a poor degree of understanding by patients receiving leaflets for hip replacements. However, these patients were given the leaflets only 24 h before operation and the content may have been difficult to read. Our experience that patients understood leaflets well is anecdotal, but compelling. Nevertheless, it is likely that some patient satisfaction comes from an appreciation of the effort to provide information as well as from improved understanding. There is no evidence so far of the effect of the leaflets on hospital complaints.

The potential of this wordprocessor system is immense and the present tendency is to expand the size of the leaflets. A pronunciation guide and spaces for questions have now been introduced and work has started towards printing diagrams with the script. Information leaflets on the disk now cover non-operative surgical topics such as the intensive care unit, breast pain, mammography, and pruritus. A French version is available. Other surgical specialities are using leaflets based on the same principles. All situations where patients require expert information about their health care could benefit from this simple technology. In conclusion, a comprehensive set of information leaflets has greatly improved general surgical patient satisfaction. The system has wide applications in other fields.

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Postscript

Details of the questionnaires and leaflets are available from the author on request.

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Original communications

Bullet emboli to the systemic and venous circulation

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The rarity of bullet emboli leads to frequent delays in diagnosis and inadequate early management. Our recent experience with this entity is described, and 153 cases reported in the English-language literature are reviewed and summarized. The majority of cases occurs as a consequence of civilian violence among men in their 20s and 30s. Most bullet emboli follow the direction of blood flow, although 15% of venous bullets cause embolization in a retrograde manner. One in 10 arterial emboli follow a right-heart or venous injury. Arterial bullets are symptomatic in 80% of cases, venous bullets in only one third. The choice of surgical management must be individualized according to the symptoms caused by the bullet and its location in the vascular system. In general, arterial bullet emboli are removed because of symptoms or findings of acute peripheral ischemia. Arterial and venous emboli not causing symptoms should be removed according to the risk of possible displacement and further embolization. Selective intraoperative angiograms and phlebograms can precisely localize the migrating bullet and permit appropriate placement of incisions before removal. (SURGERY 1990;107:239-45.)

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BULLET EMBOLI are uncommon complications of penetrating gunshot injuries. Failure to consider bullet emboli may lead to delay in diagnosis and inadequate early management that can result in loss of limb or life. This report describes our recent experience with bullet emboli and reviews 153 cases reported in the English-language literature.[1-52]

Accepted for publication May 15, 1989.

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11/56/14519

CASE REPORTS

Case 1. A 35-year-old man sustained a gunshot wound to the right upper quadrant on June 8, 1986. On admission to the emergency department his blood pressure was 110/65 mm Hg, heart rate 66 beats/min, respiratory rate 10 breaths/min. He was obtunded and underwent an immediate endotracheal intubation. No exit wound or other gunshot wound was detected. The initial x-ray film of the chest showed a bullet overlying the lower right lobe, and a right thoracostomy tube was inserted for a presumed injury to the diaphragm and right side of the chest (Fig. 1).

Exploration of the abdomen revealed that the bullet had traveled cranio-caudally through the transverse mesocolon, injuring a loop of small bowel and entering the retroperito-

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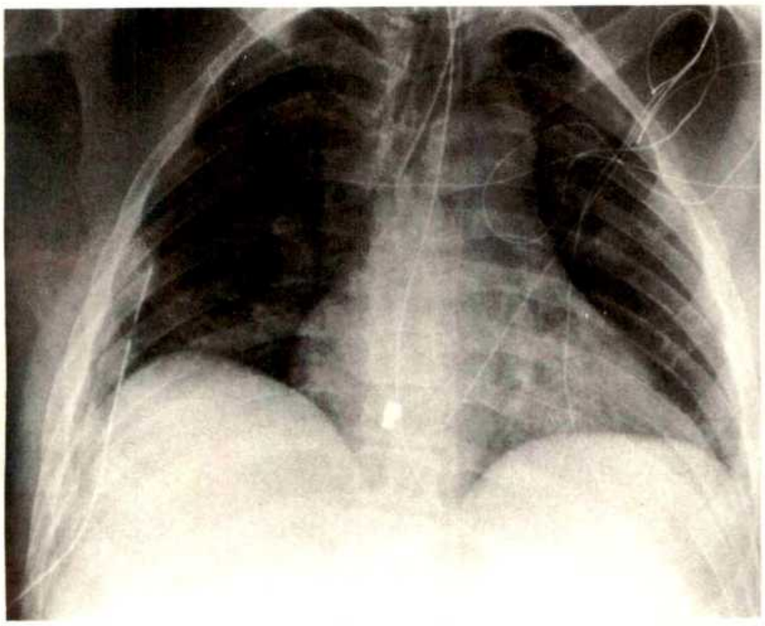

Fig. 1. Case 1. Chest x-ray film obtained in the emergency department after endotracheal intubation and insertion of a right thoracostomy tube. Note the bullet overlaying the ninth thoracic vertebra.

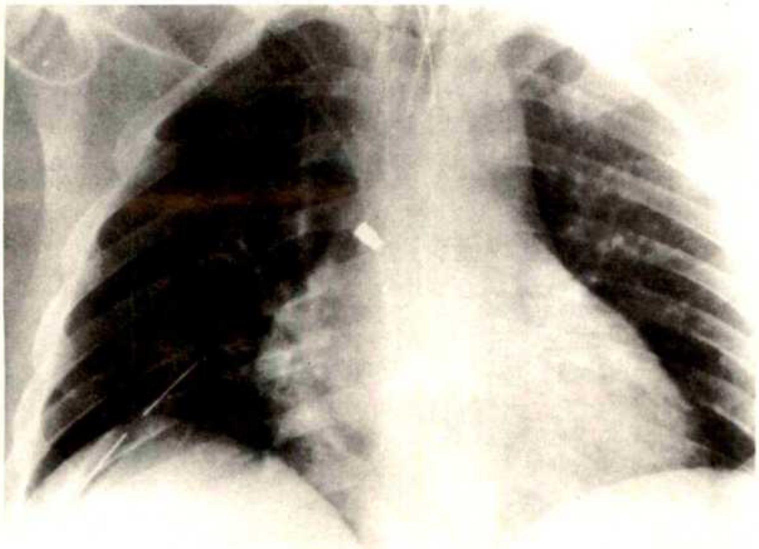

Fig. 2. Case 1. Intraoperative chest x-ray film obtained after completion of abdominal exploration. Note that the bullet has traveled to the junction of the inferior vena cava and right atrium and overlays the fifth thoracic vertebra.

neum with transection of the ureter on the right side. In view of these findings and the radiographic evidence of a supradiaphragmatic location of the bullet, a search for the entrance site in the vascular system was carefully initiated. Proximal and distal control of the inferior vena cava above the bifurcation and below the renal veins was obtained. Exploration of the inferior vena cava disclosed that the bullet had penetrated the anterior wall and then partially penetrated the posterior wall. The anterior and posterior injury to the vena cava were repaired primarily; the injured jejunum necessitated a resection and primary anastomosis; the injury to the ureter on the right side was handled with debridement and primary end-to-end anastomosis.

After completion of the abdominal exploration, a chest

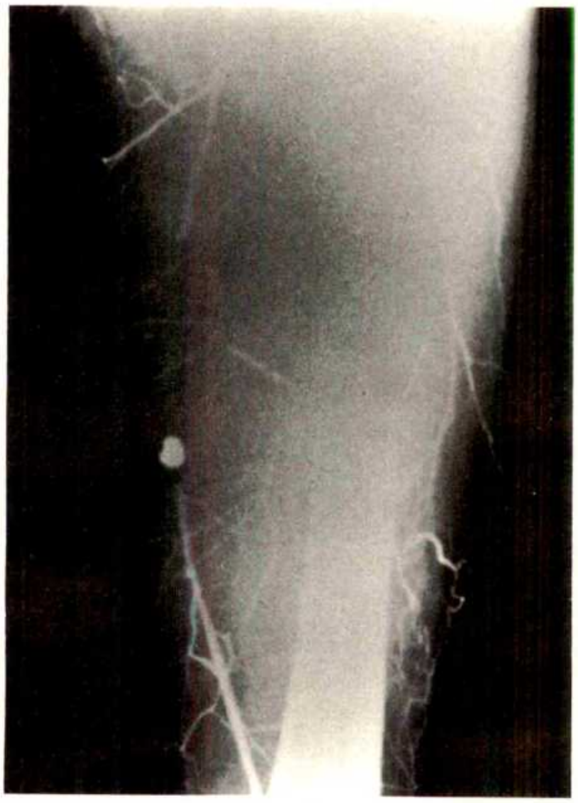

Fig. 3. Case 3. Selective arteriogram of left common femoral artery shows bullet embolus in the midportion of the left superficial femoral artery.

Table I. Entry wound

	Arterial embolism		*Venous embolism*		*Total*	
	n	%	*n*	%	*n*	%
Anterior	29	70.8	27	90.0	56	78.9
Right	12	29.3	22	73.3	34	47.9
Left	17	41.5	5	16.7	22	31.0
Posterior	12	29.2	3	10.0	15	21.1
Right	6	14.6	2	6.7	8	11.3
Left	6	14.6	1	3.3	7	9.8
Not specified	59		23		82	

Table II. Source of embolism to systemic circulation

	n	%
Thoracic aorta	22	37.9
Left ventricle	10	17.2
Abdominal aorta	9	15.5
Heart	5	8.6
Left atrium	3	5.2
Pulmonary veins	3	5.2
Right atrium	1	1.7
Right ventricle	1	1.7
Inf vena cava	1	1.7
Left com iliac a	1	1.7
Right com fem a	1	1.7
Left com carot a	1	1.7
Total	58	100
Uncertain/not specified	42	

x-ray film was taken on the operating table to precisely localize the bullet embolus (Fig. 2). The bullet was identified in a more central location, in proximity to the junction of the right atrium and superior vena cava. Through a median sternotomy, careful palpation of the superior vena cava, right atrium, and inferior vena cava did not reveal the presence of the bullet. The patient was then systemically treated with heparin, and cardiopulmonary bypass was initiated. The bullet was removed from the right atrium with digital exploration through the right atrial appendage. The patient had an uneventful postoperative course and was discharged on the ninth day.

Case 2. A 40-year-old woman sustained an air-rifle gunshot wound to the second left anterior intercostal space on Nov. 17, 1986. On admission to the emergency department, the patient was hypotensive and tachycardic. An x-ray film of the chest showed an enlarged mediastinum and a small pellet in the region of the aortic root.

An emergency median sternotomy was performed for a diagnosis of cardiac tamponade with evacuation of a large amount of blood from the pericardial space. An entrance wound hematoma was found on the anterior and left lateral aspect of the aortic root, but no exit wound was seen. Rapid hemostasis was achieved with a purse-string suture placed around the aortic wound. An x-ray film of the chest and abdomen showed that the missile had migrated from its previous location to the abdominal aorta. The median sternotomy was closed.

Fluoroscopic examination of the abdomen showed that the bullet was moving up and down along the aorta in concert with the heart rate. Two blood-pressure cuffs were then placed around both thighs in order to prevent possible embolism to the lower extremities. Attempts to retrieve the pellet with a Dormia stone basket advanced into the abdominal aorta through the right femoral artery were unsuccessful because of the continuous motion of the bullet. Finally, the bullet was pushed from the posterior wall of the aorta toward the middle of the vessel and subsequently migrated to a branch of the left internal iliac artery. The right femoral arteriotomy was closed. The postoperative course of the patient was uneventful, and she was discharged 7 days later. The patient was well 6 months after surgery.

Case 3. A 30-year-old man sustained a gunshot wound to the left flank on May 5, 1988, and was admitted with a distended abdomen, hypoactive bowel sounds, left lower quadrant tenderness, and gross blood on rectal examination. Both

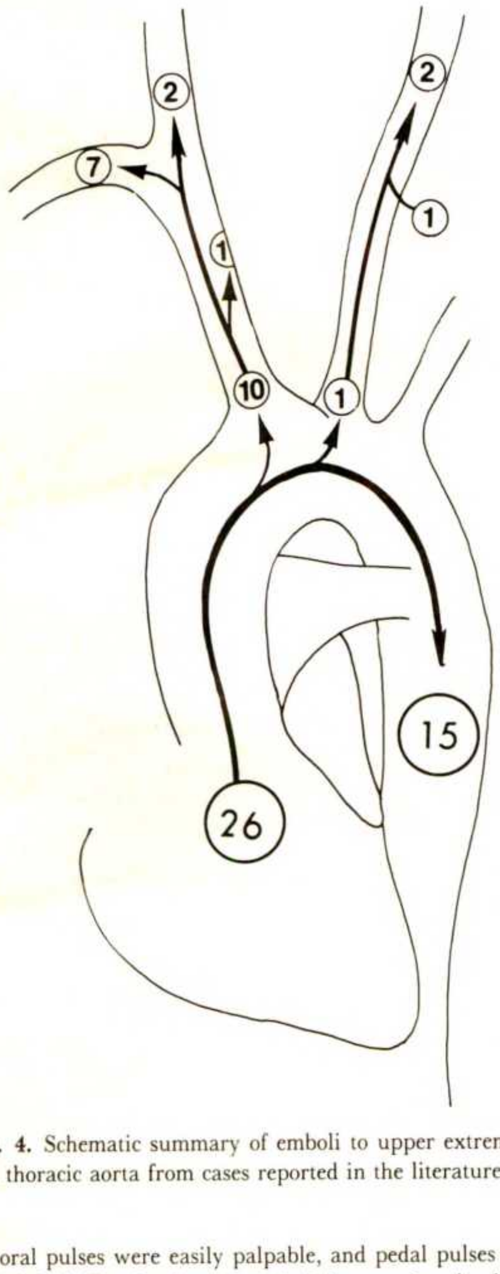

Fig. 4. Schematic summary of emboli to upper extremities and thoracic aorta from cases reported in the literature.

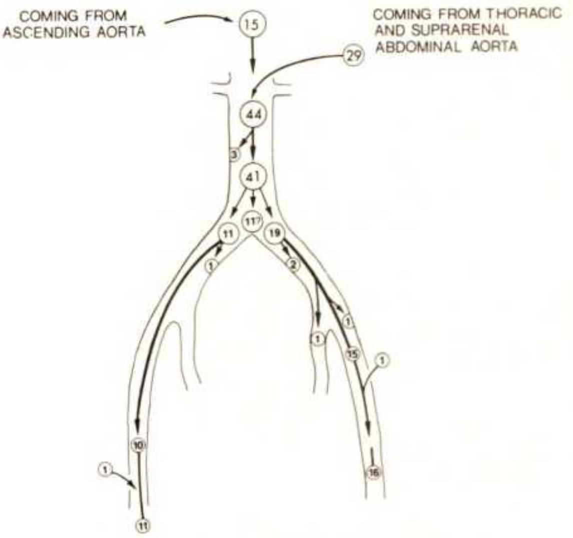
COMING FROM ASCENDING AORTA
15
COMING FROM THORACIC AND SUPRARENAL ABDOMINAL AORTA
29
44
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Fig. 5. Schematic summary of emboli to abdominal aorta and lower extremities from cases in the literature.

femoral pulses were easily palpable, and pedal pulses were diminished. Shortly after his arrival, hypotension developed, which necessitated an emergency exploratory laparotomy. A through and through injury of the descending colon and an entrance wound of the left lateral infrarenal aorta just proximal to the aortic bifurcation were found. No exit wound was discovered in the aorta. After proximal and distal control was obtained, the aortotomy was repaired primarily. The colon injury was managed by resection, descending colostomy, and Hartmann pouch. An intraoperative radiograph demonstrated a bullet in the left medial thigh. A selective arteriogram of the left common femoral artery showed that the bullet had moved to the midportion of the left superficial femoral artery, completely obstructing it (Fig. 3). The bullet was removed through a femoral arteriotomy with successful restoration of blood flow to the lower limb. The patient was discharged on the seventh postoperative day after an unremarkable recovery.

REVIEW OF THE LITERATURE

The first report of a bullet embolus is attributed to Thomas Davis, who in 1834 reported the case of a 10-year-old boy with a wooden missile fragment that moved to his right ventricle.[23] Our review of the English-language literature to January 1988 yielded 153 cases, most reported as isolated cases. Sex and age were specified in 140 and 68 cases, respectively. There were 123 male and 17 female patients, with 79.4% of patients in their second and third decades of life, reflecting a greater exposure of young men to violent penetrating trauma. Twenty-four cases were reported to occur during wartime,[12, 25, 33] and the remaining as a consequence of social violence.

The site of the entrance wound was specified in 71 cases (Table I). Fifty-six (78.9%) entry wounds were located on the anterior surface of the body. Twenty-three (56%) bullets that migrated in the systemic circulation entered to the left of the midline, whereas 24 (80%) bullets that migrated in the venous circulation entered to the right of the midline.

There were 100 cases of embolism to the systemic circulation (Table II). The site of vascular injury was in the venous circulation in three (5.2%), in the left side of the heart in 21 (36.2%), in the thoracic aorta or its branches in 23 (39.6%), and in the abdominal aorta or its branches in 11 (19%). The site of the vascular injury was not specified in the remaining 42 cases. Ten of 26

Table III. Source of embolism to venous circulation

	n	%
Inferior vena cava	7	20.6
Left iliac vein	6	17.6
Right iliac vein	4	11.8
Right atrium	4	11.8
Left pul artery	2	5.9
Right sigmoid sinus	2	5.9
Right ventricle	1	2.9
Superior vena cava	1	2.9
Sup sagitt sinus	1	2.9
Right transv sinus	1	2.9
Right axillary vein	1	2.9
Left subclavian vein	1	2.9
Left ventricle	1	2.9
Left renal vein	1	2.9
Right femoral vein	1	2.9
Total	34	100
Uncertain/not specified	19	

Table IV. Symptomatology associated with arterial and venous bullet embolism

	n	%
Arterial embolism	100	
Peripheral ischemia	30	66.7
Neurologic deficit	6	13.3
Asymptomatic	9	20.0
Not specified	55	—
Venous embolism	53	
Asymptomatic	15	65.2
Chest pain, dyspnea, hemoptisis	4	17.4
Extrasystolies	1	4.35
Arterial compression	1	4.35
Thrombophlebitis	1	4.35
Infection	1	4.35
Not specified	30	—

Table V. Treatment of bullet embolism

	Arterial embolism		*Venous embolism*	
	n	%	*n*	%
Embolectomy	35	80.0	16	61.5
Left in place	9	20.0	10	38.5
Not operated on	4	—	2	—
Not specified	38	—	19	—

bullets entering the systemic circulation migrated to the innominate artery, one entered the left carotid, and 15 proceeded along the thoracic aorta (Fig. 4). Three of 44 bullets traveling along the abdominal aorta lodged above the bifurcation, 11 coursed along the right common iliac artery, 19 proceeded along the left common iliac, and in 11 cases the pathway was not specified (Fig. 5).

The migrating bullet lodged in the venous circulation in 53 cases. The site of entrance was specified in 34 (64.2%; Table III) and was located in the heart or in the pulmonary circulation in eight (23.5%), in the inferior vena cava territory in 19 (55.9%), and in the superior vena cava in seven (20.6%). Nine (26.9%) bullet emboli lodged in the heart, trapped by the tricuspid valve, and 20 (59.6%) moved to the pulmonary arteries. The right and the left pulmonary artery were involved with about equal frequency. A retrograde embolization occurred in five cases (14.7%).

The clinical presentation is summarized in Table IV. The symptomatology associated with an arterial embolus was specified in 45% of cases and was peripheral ischemia in 67%. In the case of venous embolus, the symptomatology was specified in 43.4% of cases: two thirds of these patients had no symptoms, and one fifth had symptoms of chest pain, dyspnea, and hemoptysis.

Twenty patients (14 with arterial and six with venous bullet emboli) died of associated injuries before any surgical intervention. Treatment was specified in 48 (55.8%) of the remaining 86 patients with arterial emboli. Forty-four patients were operated on, but in only 35 (80%) was the bullet retrieved. In these cases bullet removal was mandated by signs of peripheral ischemia in 21 patients, the risk of further embolization in nine, or the need to reestablish blood flow and reverse neurologic deficits in five (Table V). Treatment was specified in 28 (59%) of the remaining 47 patients with venous emboli (Table V). Twenty-six patients were operated on, and the bullet was retrieved in 16 (61.6%) because of persisting chest pain in one patient and the risk of further embolization in the remaining 15 patients.

DISCUSSION

The occurrence of a bullet embolus is a rare event. Rich et al.[33] reported 22 such cases of bullet emboli out of 7500 vascular trauma cases occurring during the Vietnam conflict, an incidence of 0.3%. The wide use of fire weapons within the civilian population accounts for the frequency of this injury in time of peace. Only 24 of the reported cases occurred[12, 25, 33] in combat conditions, compared with 129 cases that occurred from civilian injuries.

A bullet embolus should be suspected in any patient who has a gunshot wound without an exit wound, when the signs and symptoms do not correlate with those expected from the suspected course of the missible, and when radiologic investigation shows that the missile location deviates from the supposed path of penetration. Sudden disappearance of a peripheral pulse, with or without ischemic pain, has been reported in two thirds of patients with arterial bullet emboli, whereas two thirds of patients with venous bullet emboli have no symptoms. When a bullet embolus is suspected, angiography, phlebography, pulmonary radioisotope scan, or echocardiography should be performed to confirm the location before surgical exploration, if the patient's general condition will permit the delay.

Most arterial and venous bullet emboli follow the direction of blood flow. Missiles that enter the venous system commonly migrate to the right side of the heart and frequently proceed to the pulmonary arterial tree, whereas those which enter the left side of the heart and aorta usually embolize to the upper or lower extremities (Figs. 4 and 5). Review of the literature disclosed that 14.7% of venous bullets moved in a retrograde manner, and 10.4% of arterial emboli followed a right side of the heart or venous injury. Retrograde embolization occurs because the pattern of embolization is governed by factors other than blood flow, such as body position, gravity, respiratory movements, and the missile's caliber and weight. The existence of a patent foramen ovale or the perforation of the atrioventricular septum by the bullet may account for paradoxical embolization.

Embolism in one of the branches of the aortic arch occurred in 42.3% of bullets traveling along the aortic arch. Nine of 10 bullets entered the innominate artery, probably because of its location and large caliber compared with the left carotid and subclavian artery. At the level of the aortic bifurcation, the reported incidence of embolism to the left lower extremity was twice that of the right. This may be a consequence of the asymmetry of the aortic bifurcation, which forms an angle of about 45 degrees with the midline on the right, compared with an angle of 30 degrees on the left, and confers the left common iliac artery a straighter takeoff from the aorta.

An arterial embolus causing acute peripheral ischemia should be removed as soon as possible. Indications for removing asymptomatic arterial emboli should include the risk of displacement, further embolization, proximal clot formation, and potential delayed arterial insufficiency. Arterial cerebral or pelvic emboli not causing symptoms may be left undisturbed if their removal would be technically difficult. Emboli in the vena cava or right side of the heart should be removed to avoid potential myocardial irritability, interference with valvular mechanism, and delayed migration, which may occur as long as 14 years after the trauma.[29] Asymptomatic emboli to the lung can be left in place without untoward sequelae.[23] Finally, selective intraoperative angiograms and phlebograms can precisely localize the migrating bullet and permit appropriate placement of the incision before removal.

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Correspondence

Construction of a neorectum and neoanal sphincter

Sir

Professor Williams *et al.* described in their paper (*Br J Surg* 1989; **76**: 1191–4) some problems they encountered in their patient[1]. We performed the same type of operation in three patients and would like to comment. The first case was published in 1988[2].

Electrode dislocation

We prefer intramuscular electrodes that are in common use for cardiac assist stimulation. The cathode was a screw electrode (Medtronic 6917-T, base surface 6·6 mm²) and the anode a flexible coil wire electrode (Medtronic Sp5528, bare surface adjusted with isolation sheet to about 25 mm²). We implanted the cathode in the nerve entry zone of the gracilis muscle and the anode, also in the muscle mass, a few centimeters away. (The nerve entry zone was located by assessment of the site of lowest threshold for intramuscular stimulation with needle electrodes.) With this electrode arrangement a large segment of the muscle could be activated. Electrode displacement has not occurred with this technique. The follow-up period for the first patient has been 3 years 3 months.

Stimulus frequency

Static motor units usually fire at frequencies of about 10 Hz. Therefore, several investigators used electrical stimulation at this rate for transformation of phasic units into static ones. From animal experiments cited by Williams *et al.*[1] it appeared that chronic 2 Hz stimulation resulted in this transformation. Other experiments have shown that this change also occurs with long term intermittent 40 Hz stimulation. The current state of knowledge indicates that in order to induce the transformation the artificial increase in muscle activity is more important than the stimulus frequency[3,4].

Like Williams *et al.* we found 25 Hz to be the minimum frequency at which a fused contraction could be obtained initially. The day after the implantation we started intermittent stimulation at this rate, gradually increasing the total 'stimulator-on time' per day. The advantage of starting with this frequency is that immediately after the operation the patient has a functionally normal sphincter at his disposal, which may be used for increasing periods of time. The transformation of the muscle is the result of a kind of 'in service training'. The minimum stimulation rate for fused tetanic contraction became 15 Hz (Reference 2).

Leakage and infection

Because our three patients had preserved rectal sensation, uninterrupted stimulation was not required. Usually a total stimulator-on time up to 9 h per day was sufficient to obtain complete continence. An intra-anal plug, which may have caused the inflamed perianal warts in the case of Williams *et al.* was not required in our experience. In order to prevent septic problems and possible dislocation of the distal gracilis tendon we implanted the leads and pulse generator more than 6 weeks after gracilis transposition, at which time the gracilis had proven viability. Of course Williams *et al.* had the additional problem of controlling a perineal ileostomy and we treated patients with perineal colostomy.

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Authors' reply

Sir

We were most interested to hear of the work that Baeten and Spaans have been doing on an electrically stimulated neosphincter. We apologize for not referencing their previous case report, but only became aware of it subsequent to submission of our paper. We commenced our studies independently 3 years ago both in animals[1] and man[2]. The case reported recently[3] is only one application of the concept. We have additionally created a similar neosphincter in another patient with an ileal pouch, two patients after rectal excision and coloperineal anastomosis, one patient with a failed pull-through for an imperforate anus, and nine patients with faecal incontinence.

We would concur with Baeten and Spaans that the neosphincter can deal adequately with solid faeces without the need for an intra-anal plug. Our technique, however, differs from that of Baeten and Spaans in several respects, but in particular they transpose the muscle first before implantation of the electrodes, whereas we do this at the same sitting. Secondly they use intramuscular neuronal stimulation, whereas we use direct stimulation of the nerve supplying the muscle. Although the intramuscular technique has been used for cardiac assist stimulation, the requirements for the neosphincter are different in that a virtually tetanic contraction is required of the whole muscle. The intramuscular technique by their own admission stimulates only a segment of the muscle, albeit a large one. Direct stimulation of the nerve has the advantage of activating the whole muscle. All animal experiments have used neural stimulation as intramuscular stimulation is less efficient in achieving conversion[4]. Our own animal studies, as well as confirming this fact, have shown that when intramuscular stimulation is used, a much greater voltage is required to produce the same muscular contraction, and this will significantly reduce the battery life of the stimulator. Transposition of the muscle first and delayed implantation of the electrodes makes direct stimulation of the nerve difficult. Although it would appear that Baeten *et al.* achieved success in their three patients with intramuscular neuronal stimulation, we believe that such a technique could eventually prove unreliable, because only those motor units innervated by the intramuscular branches of the main nerve in the region of the electrode will be stimulated. We should also point out that in the 14 patients so far treated by our technique, only one electrode displacement has occurred.

Baeten *et al.* transpose the muscle first, because of their concern about sepsis and muscle necrosis. This was a problem in some of our earlier patients, but we have overcome this by performing a defunctioning stoma several weeks before transposition, and at the same operation dividing the distal blood supply of the muscle. Anatomical studies[5] have illustrated that, although there is a segmental blood supply to the gracilis muscle, intramuscular arterial connections exist between proximal and distal vessel systems. Early division of the distal vessels allows these connections to open up and ensures viability of the distal half of the muscle when it is transposed. We would agree that at present the optimum stimulus parameters have not been defined. We are at present conducting a controlled trial to help resolve this problem. Baeten and Spaans commence stimulation immediately after implantation. This is not possible if the electrode is implanted at the time the gracilis is mobilized. A gap of 3 weeks is required to avoid muscular damage[6].

We note that Baeten *et al.* patients use their stimulator for approximately 9 h a day. We have also found that in the few patients with rectal sensation, intermittent use of the stimulator is possible. However, some of our patients have no sensation, and continuous use of the stimulator is required.

Despite these points, we are delighted to know that others have independently confirmed our findings, and have shown that an electrically stimulated neosphincter is feasible. Time will tell, however, whether it will be sufficiently reliable for routine use.

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Perianal condylomata acuminata

Sir

We read with interest your recent article by H. T. Khawaja[1] (*Br J Surg* 1989; **76**: 1067–8) pointing out the superior results obtained with scissor excision.

Although the natural history of *in situ* anal squamous carcinoma is unknown and despite the fact that *in situ* disease is not restricted to warts[2], we suggest that anal warts should invariably be examined histologically. Malignant transformation in these lesions is well documented[3–5]. Recognition of malignant transformation in perianal warts removed by scissor excision is impossible if excised condylomata are not examined histologically. A possible disadvantage of podophyllin is that warts are not excised for histological assessment and the influence of podophyllin on the behaviour of *in situ* carcinoma is not known.

We would be interested to know if histological assessment of the excised warts was made in this study, and if so what criteria were used to choose the warts to be examined.

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Author's reply

Sir

I wish to thank F. H. Smedley and colleagues for their comments. Histopathological diagnosis was obtained in all patients treated with scissor excision. However, only the largest of the warts from the affected anal canal and each side of the perianal area, together with any wart larger than 1 cm, were sent for examination. The site of each lesion was recorded according to its clock face position and the specimens were sent in separate pots. There was no evidence of malignant change in any of the examined lesions.

Although malignant transformation of perianal condylomata acuminata is an uncommon occurrence (1·8 per cent) in a common condition[1], I agree with Smedley *et al.* that methods of treatment which preclude histopathological assessment, such as topical drugs or fulguration, should be discouraged. There are no described criteria for selecting perianal warts for histopathological examination. The gross appearance of such lesions is an unreliable indicator of malignancy which can occur in small warts though less frequently than in larger ones[2,3]. A proposed safe practice would be to send all lesions to histology in four separate pots representing the quadrants of the clock face. This would allow more accurate localization of malignant lesions and would therefore facilitate follow-up.

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Reducing renal injury during transplantation

Sir

I read with interest the paper by J.L.R. Forsythe *et al.* (*Br J Surg* 1989; **76**: 999–1001) in which the temperature rise of cold stored kidneys was minimized during simulated transplantation by the use of a thermal insulating jacket.

The statement by these authors that: 'Other methods of keeping the kidney cool (using jackets) during the second warm ischaemic time have not met with acceptance owing to the bulk or complexity of such devices, which make the performance of vascular anastomoses more difficult', is somewhat misleading. Not cited by these authors are at least two published studies which have described thermal insulators which are neither complex or bulky.

In 1963 Markland and Parsons described the use of a jacket of neoprene rubber which was able to maintain a core temperature below 15°C for 60 min during the implantation of four human cadaver kidneys[1]. In a second study examining the warm ischaemic period in an experimental liver transplant model we concluded that two commercially available materials namely expanded polyethylene and expanded ethyl vinyl acetate represented ideal thermal insulators[2]. Because of their closed cell structure, jackets of these materials reduced core heat gain during transplantation to a mean rate of 0·1°C per minute together with the advantage of being readily vacuum moulded to assume the contour of the transplanted organ.

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Authors' reply

Sir

We thank Professor Immelman for his comments. There is no dispute that simple materials exist which adequately insulate a transplantable organ from heat gain. However, no simple device, easily applied and removed, is used routinely even in renal transplantation. This fact implies that the ideal device has not been described, as the benefits of such a device are obvious to all involved in the surgery of transplantation. The final test of an organ jacket is its regular and satisfactory use in a number of transplant centres. Since this is not the case, the quest for the ideal device must continue.

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Acute appendicitis and carcinoma

Sir

Acute appendicitis as mode of presentation of carcinoma of the caecum seems to be rare. Armstrong *et al.* (*Br J Surg* 1989; **76**: 1049–53) report a 3·4 per cent incidence in 519 patients with carcinoma of the caecum. Domerque *et al.*[1] found a 6 per cent incidence of acute appendicitis in 58 patients with colonic carcinoma who were younger than 40 years. Not only in acute appendicitis should one consider the possibility of an underlying malignancy but also in a patient who has developed a 'periappendiceal mass'. In 99 patients admitted to the Sint Franciscus Gasthuis Rotterdam between 1 January 1982 and 31 May 1987 with an initial diagnosis of periappendiceal mass we found eight patients with a malignancy of the right colon. The specimen showed tumour in the appendix in four patients and appendiceal inflammation in four patients. A correct preoperative diagnosis of colonic malignancy in these patients was made by barium enema.

Comparing this group of patients with 66 patients with a primary periappendiceal mass without malignancy, and 21 patients with a palpable right colonic malignancy without signs of inflammation lead us to the following conclusions: in any patient over the age of 50 years, with symptoms lasting over one week, in whom pain is not a predominant complaint, and with a painless palpable mass in the right lower abdomen, a barium enema must be done to rule out an underlying malignancy[2].

This will become more important as interval appendicectomy is abandoned owing to the rate of recurrent inflammation.

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1. Domerque J, Ismail M, Astre *et al.* Colorectal carcinoma in patients younger than 40 years of age. Montpellier Cancer Institute experience with 78 patients. *Cancer* 1988; **61**: 835–40.
2. Bleker R, Wereldsma J. Colonic malignancy mimicking an appendiceal mass. *Neth J Surg* 1989; **41**: 42–6.

Radionucleotide *versus* radionuclide

Sir

I enjoyed the paper by Donnelly and co-workers at the Leicester General Hospital: 'New radionucleotide method of visualizing subclavian vein occlusion following temporary venous access' (*Br J Surg* 1989; **76**: 1024–5).

I write to point out an egregious error, which surgical writers make far too often. The term 'radionucleotide' in this paper's title is just flat incorrect. A nucleotide is a compound made up of a sugar, a phosphoric acid moiety, and one of the purine or pyrimidine bases. For example, thymidylic acid, found in DNA, is a nucleotide. The authors were talking about a *radionuclide* – a radioactive element useful as a tracer in an imaging mode. They were not using radioactivity labelled genetic material as a vascular imaging substance!

I hope this commentary can be brought to the attention of the readership.

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Avascular gastric necrosis

Sir

I read with interest the recent article on postoperative gastric ischaemia (Schein M, Saadia R. *Br J Surg* 1989; **76**, 844–8). In 1967 we described ten cases of fatal anastomotic leakage due to avascular gastric necrosis, a complication of partial gastrectomy following interruption of the splenic artery or its branches[1]. If the splenic artery is eroded or the vasa brevia damaged, every effort should be made to preserve the ascending branch of the left gastric artery. If this cannot be achieved owing to proximity of the ulcer to the lesser curve, then a total gastrectomy should be performed, or else necrosis of the gastric stump risked, with ensuing peritonitis.

If erosion of the splenic artery can be recognized before ligation of the main gastric arteries then the stomach can be 'pinched off' the posterior abdominal wall and the defect closed by simple suture. A vagotomy and pyloroplasty may be added depending on the patient's condition and the surgeon's view about this procedure for the treatment of the gastric ulcer.

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1. Yeo R, Powell K. Avascular gastric necrosis – a complication of partial gastrectomy following interruption of the splenic artery or its branches. *Br J Surg* 1967; **54**: 707–9.

Complications of parotid surgery

Sir

In their enthusiasm for more limited parotid surgery I fear that Owen *et al.* have been less than rational (*Br J Surg* 1989; **76**: 1034–5).

In using a 9 per cent permanent facial palsy rate as a reason for less radical surgery they have missed the point. Of their ten patients with a permanent palsy six had deliberate sacrifice of the nerve as it passed directly into the tumour. The remaining four had a deep lobe tumour. In neither circumstance would more conservative surgery have prevented the complication described.

The second point with which I take issue is the classification used. They appear to accept that the pleomorphic adenoma is other than a benign condition. It may at times become malignant and it does have a propensity to recur locally but histologically it is undoubtedly a benign tumour. To suggest otherwise is to encourage the use of inappropriate treatment such as enucleation followed by radiotherapy.

I remain unconvinced that fine needle aspiration cytology followed by more selective surgery is the treatment of choice. The possibility of two tumour types (monomorphic adenonoma and pleomorphic adenoma) being present in the one gland is well recognized. In a series of 130 parotidectomies I have had just such a case. That occurrence does not persuade me that fine needle aspiration cytology is infallible or indeed necessary.

N. MacGillivray

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Authors' reply

Sir

As a general principle we make a precise diagnosis before the operation to obtain a plan based on the pathology. This is particularly true in ablative cancer surgery and should apply to the parotid.

The very reason for advocating precise distinction between benign and malignant lesions is the unnecessarily high incidence of temporary and permanent facial nerve palsy in otherwise benign pathology (36 per cent temporary and 8 per cent permanent). Of the ten patients with permanent palsy, five had histologically proven benign pathology. If these five patients had had limited less radical surgery (or none at all) the nerve would not need to have been divided outside the capsule. The phrase 'passing directly into the tumour' indicated that in a wide extra-capsular excision the nerve was too close not to sacrifice.

In our view a pleomorphic adenoma is a locally malignant tumour needing wide extra capsular excision in every case.

We accept the rare occurrence of dual pathology (mono and pleomorphic) in one gland; the incidence of 1 in 130 cases is an index of how unusual it is. Although Mr MacGillivray is unconvinced we would like to have evidence for his reasons.

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Treatment of carcinoma of the breast

Sir

We read with interest the paper by Reed and Morrison (*Br J Surg* 1989; **76**: 898–900). Acknowledging that the treatment of elderly patients with breast cancer and the use of adjuvant therapy is changing, several comments need to be made.

Ninety-six patients were studied over a 15-year period which represents one patient every 2 months. The data have been analysed four years after the close of the study but mean follow-up is only 47 months. Can the authors reassure us of the uniform accrual of patients into this study without selected exclusions? Follow-up data were only available in 88 patients further reducing numbers and the ability to make meaningful analyses. How were locoregional recurrences determined especially in the light of the information of 14 per cent of the patients having clinically involved nodes? Were these locoregional recurrences in addition to the clinically involved nodes and how was recurrence proved?

Figure 1 is misleading, suggesting that there was no difference in overall survival between those with or without recurrence because of deaths owing to unrelated causes. No life table analysis was carried out and we are unable to assess overall differences in survival which may exist. It is surprising that there were no non-breast cancer deaths among those with recurrent disease especially in view of the age group studied.

We are unsure of the meaning of 'the risk of breast recurrence tended to increase with increasing size (presumably tumour size), a trend that was not seen with systemic recurrence'. How can any statement be made on these patterns with the numbers displayed in *Table 3* when one of four patients with breast recurrence is 25 per cent?

The criteria for the selection of patients for conservative surgery have been previously described by numerous authors and ironically are presented by Locker *et al.* in the same issue (pages 890–4). There can be no doubt that radiotherapy reduces the risk of local recurrence after conservation surgery and it is likely that node positive patients should either be excluded or receive adjuvant chemotherapy in addition[1]. Failure to employ radiotherapy in the present study has led to a high (35 per cent) local recurrence rate which has occurred early in follow-up (mean 31 months). The authors seem to refute many previous findings without data to support their claims. Tumour size (>5 cm) and the presence of palpable axillary nodes (no mention of histological status) is said not to have affected locoregional recurrence rates in this study but this can only be due to the small numbers assessed (four patients with tumours >5 cm and 13 with involved nodes).

Tamoxifen is now established as an adjuvant therapy in patients with operable breast cancer[2] and it appears useful as a primary therapy in elderly patients[3] who are more likely to have oestrogen receptor positive tumours. Failure to use tamoxifen as therapy in the elderly cannot be considered acceptable practice. Newer methods for identifying tumours which will respond to tamoxifen may refine selection in the elderly[4].

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1. Fisher B, Redmond C, Poisson R *et al.* Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1989; **320**: 822–8.
2. Early Breast Cancer Trialists Collaborative Group. Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer: an overview of 61 randomized trials among 28 896 women. *N Engl J Med* 1988; **319**: 1681–92.
3. Gazet J-C, Markopoulos CH, Ford HT, Coombes RC, Bland JM, Dickson RC. Prospective randomized trial of tamoxifen *versus* surgery in elderly patients with breast cancer. *Lancet* 1988; **i**: 679–82.
4. Nicholson S, Halcrow P, Sainsbury JRC *et al.* Epidermal growth factor receptor (EGFr) status associated with failure of primary endocrine therapy in elderly postmenopausal patients with breast cancer. *Br J Cancer* 1988; **58**: 810–4.

APACHE II in massive upper gastrointestinal haemorrhage from peptic ulcer

Sir

We read with interest the review article by Evans (*Br J Surg* 1989; **76**: 1311–15). The author criticizes our study on the use of APACHE II in massive upper gastrointestinal haemorrhage from peptic ulcer[1], accusing us of having committed a type III error. It seems that the author herself has fallen victim to the same error by drawing inappropriate conclusions from the reading of our manuscript.

It is true that originally the APACHE II scoring system was not designed to stratify individual patients before operation. However, our data show that the use of APACHE II can introduce an objective perspective into the measurement of acute surgical diseases and improve surgical decision making. Our study did not claim to be anything but retrospective with the accepted inherent limitations. It constitutes a first step in the right direction. Since then we have validated our initial results in a prospective series of 25 patients (*Table 1*).

Now to the comment that APACHE II cannot be determined in less than half an hour in most hospitals (does this include the author's hospital?). We feel that if vital signs determination, full blood count, electrolytes and creatinine (or urea) measurement and an urgent arterial blood gas cannot be performed urgently (all that is needed for APACHE II scoring), then acutely ill patients should be treated elsewhere.

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1. Schein M, Gecelter G. APACHE II score in massive upper gastrointestinal haemorrhage from peptic ulcer: prognostic value and potential clinical applications. *Br J Surg* 1989; **76**: 733–6

Table 1 APACHE II scores and associate mortality in patients operated for bleeding gastric and duodenal ulcers

	Scores					
	0–10		11–20		21–25	
	No. of patients	Mortality	No. of patients	Mortality	No. of patients	Mortality
Retrospective data[1]	20	0(0)	82	15 (18)	6	4(67)
Prospective data (unpublished)	8	0(0)	14	3(21)	3	2(67)

Values in parentheses are percentages

Book reviews

A Colour Atlas of Chest Trauma and Associated Injuries. Volumes 1 and 2

A. Besson and F. Saegesser. 265 × 200 mm. Pp. 384 (Volume 1) and 336 (Volume 2). Illustrated. 1982. London: Wolfe Medical Publications. £65.00 each.

Dr Besson and Dr Saegesser have used experience gained from management of serious chest trauma at the Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (largely between 1962 and 1972) to illustrate the nature, presentation and management of chest injuries. Much of the trauma is the consequence of road traffic accidents; stab wounds, bullet wounds and blunt injuries are included to give a representative profile of chest trauma as seen in contemporary civilian practice.

Perhaps the most striking impression is the fascination and interest the books evoke. The authors manage to convey a realistic picture of chest injuries by the use of illustrations of the causes (often the wreck of a car), the clinical features, radiological appearances, and operative findings. The main thrust of the text is the provision of clear, practical guidelines to management, and this includes complications, iatrogenic injuries and unsuccessful outcomes. The explanations of the nature of the forces encountered during deceleration injuries and the destructive power of high speed missiles add to the understanding of the clinical presentation and management.

It is repeatedly emphasized that chest injuries are often but part of more widespread injury. Frequent reference is made to the principles of managing the multiply injured patient in the context of major chest trauma. Both volumes are necessary – the first deals with deceleration, penetrating and blunt injuries, fluid collections in the chest (with a commendable section on drainage bottles and suction systems) and pulmonary trauma; the second deals with individual thoracic viscera.

On the basis of the extensive database which supports this work the authors have given a detailed breakdown of the prevalence of other injuries associated with specific chest injury, as well as a careful analysis of likely outcome. There is a good reference list for each chapter. Though published in 1982 and 1983, little is out of date. These volumes should be seen as complementary to standard texts and review articles; their graphic and clear message would be hard to beat in words alone. They can be recommended highly to surgeons, anaesthetists and all involved in the management of major injury.

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Splanchnic Ischaemia and Multiple Organ Failure

A. Marston, G. B. Bulkley, R. G. Fiddian-Green and U. H. Haglund. 250 × 195 mm. Pp. 405. Illustrated. 1989. London: Edward Arnold. £65.00.

This is an interesting book which describes mesenteric ischaemia, ischaemia of the liver and pancreas and multiple organ failure after cardiac surgery. There is a subsection on the mechanisms of ischaemia injury including free radicals and reperfusion injury written by the acknowledged expert Neil Granger. There are other sections on acute acalculous cholecystitis, and on clinical care in the intensive care unit. The book was derived from a symposium and it does have that slight symposium feel although it has been well produced. I am doubtful if many surgeons will want to purchase this book, but it is obviously an extremely important reference source for those interested in splanchnic ischaemia. The general feel of the book is of a research tome being extremely well referenced and for the most part easy to read. The price is £65.00. I have no hesitation in commending it.

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Organ Transplantation: Current Clinical and Immunological Concepts

L. Brent and R. A. Sells. 250 × 175 mm. Pp. 299. Illustrated. 1989. London: Baillière Tindall. £35.00.

The concept underlying this volume is familiar, but there are unusual additions. The main part is essentially a collection of invited essays by leading authorities in various fields related to organ transplantation. This format is the simplest to organize, but unless the Editors are rigorous the result is inevitably considerable repetition, albeit with a different slant from each author. In the present volume the mechanisms of graft rejection are discussed under at least three headings, with different versions presented in each. This does give the correct impression that the subject is far from closed, but may confuse the unitiated. Some of the chapters are of high quality; I particularly liked the contribution from Rubin and Cosimi on immunosuppressive and antimicrobial therapy. A foray into molecular biology is also welcome. Unfortunately not all the authors have made quite the same effort.

The interesting additions include a large section summarizing the important clinical data from the registries of the various organ grafts and a section on international transplantation statistics. Most of the data presented are available elsewhere, but it is convenient to have the important facts in one edition, notwithstanding the inevitable loss of immediacy caused by the publishing lag time. A very nice touch is the addition of a historical section with brief accounts of milestones in transplantation, including key references. Although the preface expresses the hope that the book will appeal to a wide audience, I suspect it will be of interest mainly to those established in the field of transplantation.

D. W. R. Gray

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Aortic Surgery

J. J. Bergan and J. S. T. Yao. 260 × 185 mm. Pp. 574. Illustrated. 1989. Philadelphia: W. B. Saunders. £66.00.

John Bergan and James Yao are among the most experienced of vascular surgical Editors and this volume on aortic surgery does them great credit. It is, quite simply, excellent and I would recommend it to all surgeons interested in arterial work.

There are 40 chapters covering all aspects of aortic disease, its treatment, and possible complications. As well as sections on the expected disease entities, conditions such as arteriomegaly and embolism from the aorta are dealt with individually and well. There are specific chapters on the merits and techniques of combining coronary, lower limb, and non-vascular procedures with aortic reconstruction, and on the options to conventional aortic bypass grafting. Complications given chapters of their own include acute limb ischaemia and urological injuries, in addition to later problems such as infected grafts, fistulae, and sexual dysfunction.

The consistently high quality of this multi-author book is impressive. The chapters are relevant, practical, and well referenced. Each author has presented a global view of his subject rather than just the stilted personal series sometimes found in collected works of this kind.

The Editors have engineered not only a collection of informative reviews, but also a good technical handbook for aortic surgery and a useful reference source. I can see little competition for this book as a comprehensive yet concise work on aortic surgery.

B. Campbell

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Notices and announcements

19–20 April 1990
General Thoracic Surgery
Las Vegas, USA
Information: American College of Chest Physicians, PO Box 93826, Chicago, Illinois 60673, USA

27–28 April 1990
The 3rd International Symposium on Gynaecological Endoscopy
Oxford, UK
Information: Metaphor Conferences & Meetings, 21 Kirklees Close, Farsley, Pudsey, West Yorkshire LS28 5TF, UK

2–4 May 1990
17th Biennial Congress of the Association of Surgeons of South Africa in Bloemfontein
Bloemfontein, South Africa
Information: Dr GF Ferreira, Dept of Surgery, (G72) Univ. of the OFS, Box 339, Bloemfontein 9300, Republic of South Africa

9–12 May 1990
3rd International Symposium on Echocardiography and Doppler in Cardiac Surgery
Vienna, Austria
Information: W. Mohl, c/o Interconvention, A-1450 Vienna, Austria, +43/1/23 69/2642

12–15 May 1990
Second Annual UCLA Extension Program on Endovascular Surgery
Beverly Hills, USA
Information: UCLA Extension, Post Office Box 24901, Los Angeles, CA 90024-0901, USA

16–18 May 1990
Blood Vessel Imaging Using Ultrasound Techniques
Southampton, UK
Information: Mr K. N. Humphries, Blood Vessel Imaging Course, 10 Swale Drive, Chandlers Ford, Hampshire SO5 3QY, UK

17–19 May 1990
The First French Symposium on Hernia Surgery
Nice, France
Information: Dr G. Dieudonne, Institut Arnault Tzanck, Avenue du docteur Maurice Donat, 06700 Saint-Laurent Du Var, France

23–26 May 1990
Eighty-First Annual Meeting of the American Association for Cancer Research
Washington DC, USA
Information: American Association for Cancer Research, 330 Market Street, 2nd Floor, Philadelphia, PA 19106, USA

24 May 1990
British Association of Endocrine Surgeons Meeting
London, UK
Information: Mr A. W. Goode, Hon. Secretary, British Association of Endocrine Surgeons, The London Hospital, London E1 1BB, UK

27–29 May 1990
International Symposium: Challenges in Vascular Surgery
Norway
Information: Secretariat, Dept of Vascular Surgery, Aker Hospital 0514, Oslo 5, Norway

29 May–1 June 1990
Peripheral Vascular Disease
London, UK
Information: The British Council, Courses Department, 65 Davies St, London W1Y 2AA

3–8 June 1990
Third World Congress on HPB Surgery
London, UK
Information: HPB Congress Secretariat, Congress House, 65 West Drive, Sutton, Surrey SM2 7NB, UK

5–9 June 1990
European Association for Gastroenterology & Endoscopy: European Digestive Disease Week
Vienna, Austria
Information: Mondial Congress, Faulmanngasse 4/11 A-1040 Wien, Austria

8–9 June 1990
3rd Annual Meeting of The Surgical Infection Society
Antwerp, Belgium
Information: Professor A. Hubens, University Dept of Surgery, Stuivenberg General Hospital, Lange Beeldekenstraat 267, B-2008 Antwerp, Belgium

11–14 June 1990
Current Techniques in Hepatic and Gastrointest. Research
London, UK
Information: Judit Ashton, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN

11–14 June 1990
6th International Congress on Breast Diseases
Boston, Massachusetts, USA
Information: 6th International Congress Secretariat, c/o Office of Continuing Education, Tufts University School of Medicine, 136 Harrison Avenue, Box 36, Boston, MA 02111, USA

13–16 June 1990
5th European Symposium on Gastrointestinal Motility
Augsburg, FRG
Information: Professor M. Weinbeck, Dept. of Internal Medicine III, Zentralklinikum, D-8900 Augsburg, FRG

20–23 June 1990
Annual Meeting of The Endocrine Society
Atlanta, Georgia, USA
Information: Ann Singer, Meetings Manager, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

24–28 June 1990
XIII Biennial Meeting of I.S.U.C.R.S.
Graz, Australia
Information: Miss D. Strauss, Executive Secretariat, c/o Indru T. Khubchandani, 1275 S. Cedar Crest Boulevard, Allentown, PA 18103, USA

24–29 June 1990
The 3rd Oxbridge Organ Transplantation Course
Oxford, UK
Information: British Council Office, Courses Department, 65 Davies St, London W1Y 2AA

25–27 June 1990
Three day course in hyperlipidaemia
London, UK
Information: Judit Ashton, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN

5–6 July 1990
Surgical Research Society Meeting
Southampton, UK
Information: Mr C. D. Johnson, University Surgical Unit, Centre Block 'F' Level, Southampton General Hospital, Tremona Road, Southampton SO9 4XY, UK

12–14 July 1990
XVth International Update on Liver Disease
London, UK
Information: Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

14–15 July 1990
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

15–21 July 1990
1990 Surgical Updating
Milan, Italy
Information: Segreteria Organizzativa, MGR, Via Servio Tullio, 4-20123 Milano, Italy

22–27 July 1990
FASEB Summer Research Conference 'Physiology and Pathophysiology of the Sphlanchnic Circulation'
Colorado, USA
Information: Federation of American Societies for Experimental Biology, Splanchnic Circulation Conference, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

25–27 July 1990
British Association of Paediatric Surgeons XXXVII Annual International Congress
University of Strathclyde, Glasgow, UK
Information: Miss D. Grant, BAPS Administrative Secretary, Royal College of Surgeons, Nicolson Street, Edinburth EH8 9DW, UK

22–24 August 1990
International Hepato-Biliary Pancreatic Assoc. 12th Annual Meeting
Hong Kong
Information: The Secretariat, IHBPA Hong Kong, Department of Surgery, Queen Mary Hospital, Hong Kong

20–21 September 1990
IV Annual Meeting of the European Society for Vascular Surgery
Rome, Italy
Information: Paolo Fiorani, Department of Vascular Surgery, University of Rome, School of Medicine, Policlinico Umberto 1, 00161 Rome, Italy

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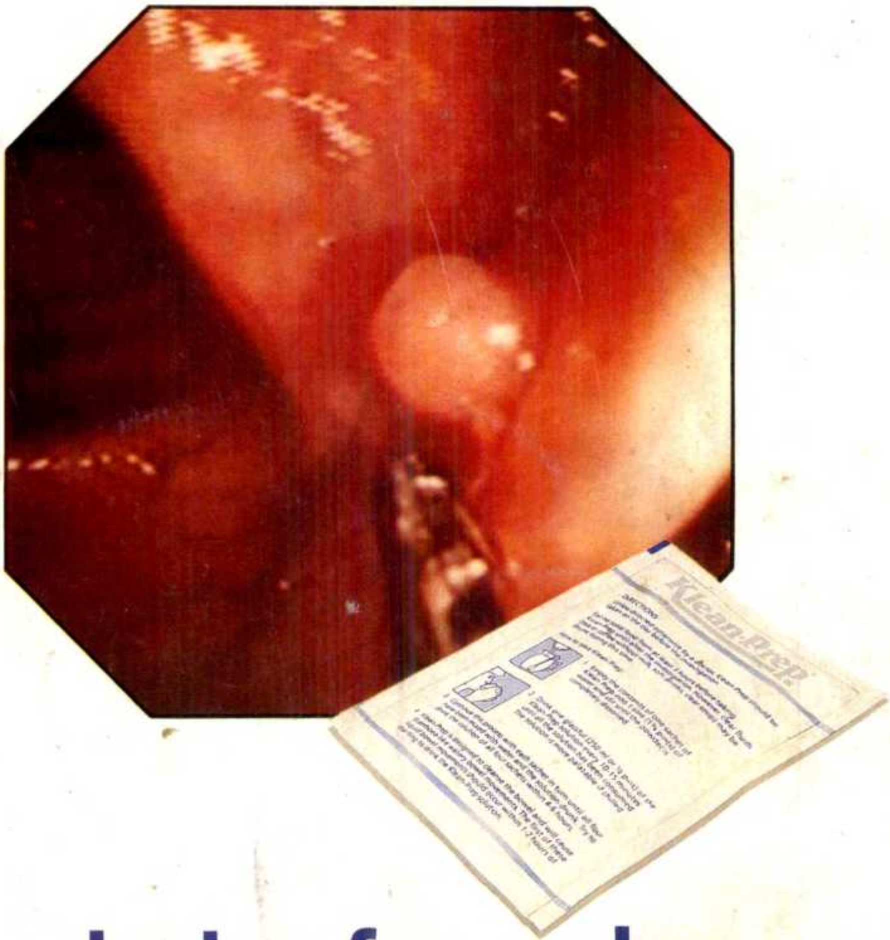

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